DOCTORAL THESIS

Efficiency of Stereoselective [2,3]-Sigmatropic Rearrangement Reactions

Aleksandra Murre

TALLINNA TEHNIKAÜLIKOOL
TALLINN UNIVERSITY OF TECHNOLOGY
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TAL TECH PRESS

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Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

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ALEKSANDRA MURRE

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Contents

List of publications

The list of author's publications, on the basis of which the thesis has been prepared:

I Murre, A.; Erkman, K.; Kaabel, S.; Järving, I.; Kanger, T. Diastereoselective [2,3]-Sigmatropic Rearrangement of *N*-Allyl Ammonium Ylides. *Synthesis* **2019**, *51*, 4183–4197.

II Murre, A.; Erkman, K.; Järving, I.; Kanger, T. Asymmetric Chemoenzymatic One-Pot Synthesis of α-Hydroxy Half-Esters. *ACS Omega* **2021**, *6*, 20686–20698.

III Murre, A.; Mikli, V.; Erkman, K.; Kanger, T. Primary Amines as Heterogeneous Catalysts in an Enantioselective [2,3]-Wittig Rearrangement Reaction. *iScience* **2023**, *26.*

Author's contribution to the publications

Contribution to the papers covered by this thesis are:

I The author made substantial contributions to the development of the synthetic methodologies. The author played a significant role in the synthesis and characterisation of all compounds essential to this study. The author played a minor role in the manuscript preparation and compiled the supporting information.

II The author played a major role in the development of the synthetic methodologies, and in the synthesis and characterisation of all compounds essential to this study. The author prepared the manuscript and compiled the supporting information.

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Introduction

Sustainability plays a pivotal role in shaping our present and future. Nowadays, it has become an essential concept that overall encompasses responsible practices and resource management. Chemistry heavily influences our daily lives, shaping the materials we use, the energy we consume, and the medications used to treat us. Yet, this omnipresence comes at a price, as chemical processes and products have been historically associated with adverse environmental and health impacts. This paradox, the duality of chemistry as both a potent enabler and a significant environmental burden, has spurred the emergence of green chemistry principles, which align with the United Nations Sustainable Development Goals.

The achievement of these sustainability goals requires re-evaluation and re-structuring of existing chemical reaction pathways into more streamlined and sustainable reactions. By ensuring that most of the atoms from the starting materials are incorporated into the desired products, rearrangement reactions reduce the generation of undesirable by-products, inherently contributing to cleaner and more sustainable processes. Not only are rearrangement reactions atom-efficient but they can also be used to generate compounds with multiple stereogenic centres, making them valuable tools for producing chiral molecules with high efficiency. However, it is critical to acknowledge that efficiency in chemistry is not an endpoint but an ongoing process of improvement.

This doctoral thesis aims to contribute not only to the advancement of synthetic methodologies but also to the broader goals of sustainable and responsible chemistry. By addressing such aspects as time consumption, sequential derivatisation of the intermediate without isolation and catalyst sustainability, we endeavour to refine rearrangement reactions into more efficient, eco-friendly and economically viable tools for the synthesis of valuable compounds (**Publications I** – **III**). The effects of bases on the diastereoselectivity of the [2,3]-sigmatropic rearrangement reaction of *N*-ammonium ylides was studied (**Publication I**). Subsequently, the investigation of the asymmetric [2,3]-Wittig rearrangement reaction of malonic derivatives in combination with enzymatic hydrolysis was undertaken (**Publication II**). This was followed by an examination of the catalyst's recyclability utilised in the [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives (**Publication III**).

Abbreviations

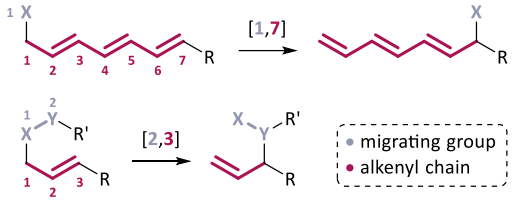
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BTM	benzotetramisole
CALB	Candida antarctica: lipase B
conv.	conversion
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIC	*N*,*N*'-diisopropylcarbodiimide
dif.	different
DMC	dimethyl carbonate
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent
Et	ethyl
EWG	electron-withdrawing group
Fmoc	fluorenylmethoxycarbonyl
h	hour
HOBt	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
*i*Pr	isopropyl
IR	infrared
LB	Lewis base
LDA	lithium diisopropylamide
major dr	major diastereomer
Me	methyl
min	minute
minor dr	minor diastereomer
*n*Bu	normal butyl
nd	not determined
NMR	nuclear magnetic resonance
Nu	nucleophile
OPNP	*p*-nitrophenoxide

PAM	*p*-hydoxymethylphenylacetamidomethyl polystyrene
PB	phosphate buffer
PG	protecting group
Ph	phenyl
PLE	pig liver esterase
p-NBA	*p*-nitrobenzoic acid
PS	polystyrene
rac	racemic
Rf	retention factor
RML	Rhizomucor miehei
rt	room temperature
SEM	scanning electron microscopy
TB	Tris buffer
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
*t*Bu	*tert*-butyl
TEA	triethylamine
TfO	trifluoromethanesulfonate / triflate
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl
TS	transition state
U	unit/mg

1 Literature overview

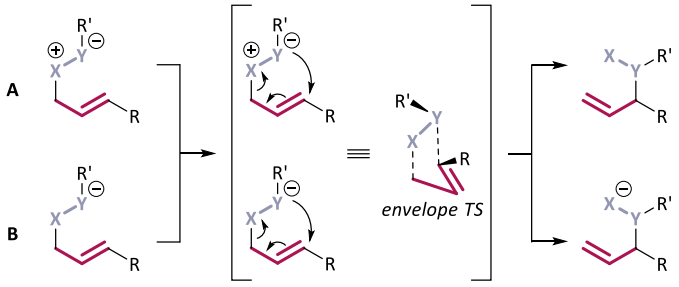
Sigmatropic rearrangements are well-known substrate-reorganisation reactions that represent a valuable technique to construct novel complex molecules.[1] The relocation of a σ-bond from one position of a π-system to another allows for the formation of a new carbon-carbon or carbon-heteroatom bond in an intramolecular manner. As during sigmatropic rearrangement the migration of an atom or a group occurs within the same molecule without changing the composition of the product, this type of reaction is 100%-atom efficient.[2]

Sigmatropic rearrangement reactions can be classified by the order which characterises the shifting of the migrating group. This depends on the original and terminal position of the σ-bond.[1,3] A numeric prefix [a,b] identifies the number of atoms of the migrating group (a) and the conjugated alkenyl chain (b) between the ruptured and newly created bonds (Scheme 1).[4] In this work, [2,3]-sigmatropic rearrangement reactions were studied, and therefore an overview of only this type of rearrangement is given.



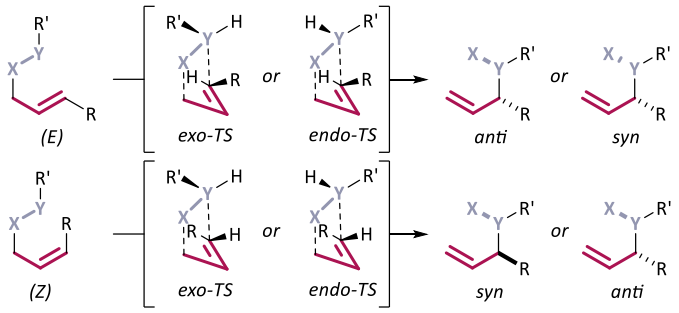
Scheme 1 *Examples of the formation of the numeric prefixes in sigmatropic rearrangements*

In general, [2,3]-sigmatropic rearrangements are divided into two categories: neutral (Scheme 2, A) and anionic (Scheme 2, B). In both cases, the reaction proceeds via a five-membered pericyclic envelope-like transition state. The main difference between these two lies in the charge nature of the X-Y pair of the rearrangement precursor. The neutral type includes the rearrangement of zwitterionic species.[5] In contrast to the neutral type, the anionic type first includes the generation of a carbanion, which then undergoes a rearrangement reaction.[6] The formation of a carbanion is mainly facilitated by using an electron-withdrawing group (R') via contributing to the deprotonation step of the reaction.



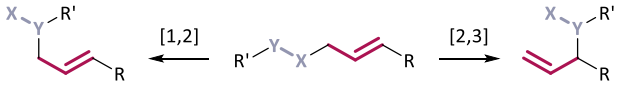
Scheme 2 *General mechanism of neutral and anionic [2,3]-sigmatropic rearrangements*

Rearrangement reactions are especially valuable transformations for the introduction of an additional complexity to the molecules as, depending on the substituents, up to two new consecutive stereogenic centres can be simultaneously formed.[7] In many cases, a well-defined transition state of the [2,3]-sigmatropic rearrangement reaction leads to highly controlled stereospecificity in terms of diastereoselectivity. Starting materials bearing double bonds in (*E*) configuration tend to undergo rearrangement reactions via an *exo*-transition state, affording *anti*-products, while compounds with a double bond in the (*Z*) configuration prefer to follow an *endo*-transition state, therefore giving *syn*-products (Scheme 3). The differences in energy between *exo*- and *endo*-transition states determine the final ratio of diastereomers. This is strongly dependent on both steric and electronic interactions between the migrating moiety and electron-withdrawing group R′ in the transition state. In addition, the diastereoselectivity of the [2,3]-sigmatropic rearrangements is strongly influenced by the properties of the substituents.[5,8,9] Enantiocontrol of these rearrangement reactions is less defined, as the origin of the enantioselectivity depends on the precise type of stereoinduction used to achieve it.



Scheme 3 *General representation of the dependence of diastereoselectivity on the double bond configuration of the starting material*

The possibility of a competing [1,2]-pathway instead of the [2,3]-sigmatropic rearrangement should also be considered (Scheme 4). These two types of rearrangement reactions proceed through different mechanisms. The [1,2]-pathway is believed to be a stepwise process, where homolysis of the C-X bond takes place followed by the recombination of the formed radical species. As the [2,3]-rearrangement proceeds via a concerted mechanism with lower activation energy, the [1,2]-rearrangement is rarer and can be suppressed or eliminated by substrate design and the careful tuning of reaction conditions.[1]



Scheme 4 *Competing [1,2]- and [2,3]-sigmatropic rearrangements*

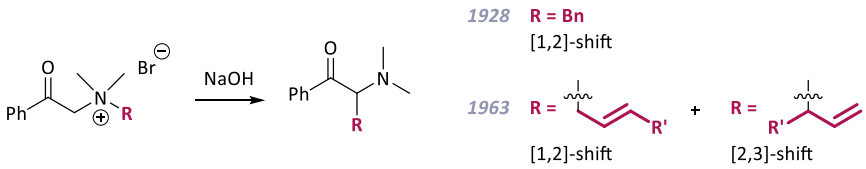
1.1 [2,3]-Sigmatropic rearrangement of ammonium ylides

[2,3]-Sigmatropic rearrangements of different zwitterionic species are a diverse class of [2,3]-shifts and have been well explored. Reactions can be conducted with substrates usually formed from various oxides (*e.g.* allylic sulfoxides[10], selenoxides[11] and amine oxides[12]) and "onium" salts traditionally generated using alkylation methods (*e.g.*

ammonium, sulfonium, phosphonium, oxonium and halonium)[13]. In continuation, the metal-carbene complex approach follows the same principle. However, it utilises a completely different type of mechanism for the initialisation of the rearrangement reaction, leading to the direct formation of the allylic "onium" ylides *in situ* through a transition-metal-catalysed decomposition of diazo compounds[14]; thus, it falls outside the scope of this work.

In this doctoral thesis, the neutral type of [2,3]-sigmatropic rearrangement is represented by the diastereoselective base-catalysed transformation of the ammonium ylides as a valuable method for the construction of tertiary nitrogen-containing molecules. Thus, only examples connected with this topic are included in the literature overview, excluding the Sommelet-Hauser rearrangement[15] of *N*-benzylic quaternary ammonium salts.

The great potential and the reactivity of the ammonium ylides were first introduced by Stevens *et al.* in 1928.[16] During their investigation into various amino-protecting groups, a [1,2]-shift of the benzylic moiety occurred under basic conditions. The described migration is now known as the [1,2]-Stevens rearrangement.[17] In this particular case, the formation of the adduct from the [2,3]-sigmatropic pathway, known as the Sommelet-Hauser rearrangement, was not observed, despite its potential as a competing reaction pathway, wherein the deprotonation of benzylic CH_2 initiates migration through an aromatic double bond, followed by the introduction of a novel alkyl group in the ortho position of the benzylic substituent. Notably, the [2,3]-shift was first observed in 1963 as a competitive side-reaction to the [1,2]-Stevens rearrangement. While exploring the analogous allyl-substituted ammonium salts, the appearance of the product, which was confirmed to follow a [2,3]-sigmatropic pathway, was also detected (Scheme 5).



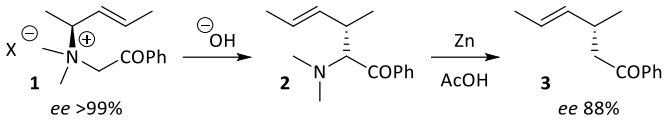
Scheme 5 *The historical background of [1,2]- and [2,3]-sigmatropic rearrangements of ammonium ylides*

Since then, tremendous developments in this field have occurred, especially from the perspective of stereoselectivity. In principle, there are two general methods for influencing diastereo- and enantioselectivity in rearrangement reactions. Either already existing chiral centres and/or the bulkiness of the substituents of the starting material direct the formation of the new stereogenic centre through steric effects (substrate control) or an external compound provides stereoinduction via coordination with a substrate (reagent control). Notably, the [2,3]-sigmatropic rearrangement of ammonium ylides lacks examples of the second approach. Most likely, this is due to the absence of an electron pair on the quaternary nitrogen, which is essential for the chiral reagent to coordinate with the substrate and, therefore, direct the stereoselective outcome of the reaction.[18]

1.1.1 Base-catalysed rearrangement originating from chiral ammonium salts (based on the chirality transfer principle)

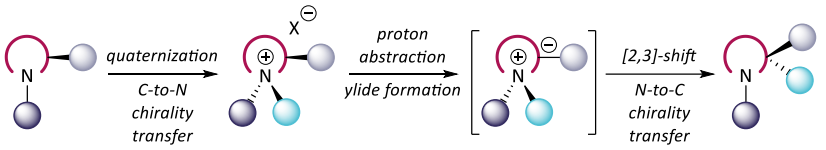
In many cases, highly diastereoselective outcomes of the [2,3]-sigmatropic rearrangement of the ammonium ylides were achieved through chirality transfer from the starting material.

A successful example of chirality transfer from the C1 position of an enantiomerically enriched ammonium salt **1** (*ee* >99%) to the C3 position was demonstrated by Hill *et al*. Reductive cleavage of the amino moiety from the rearranged product **2** afforded ketone **3** with slightly diminished enantioselectivity (*ee* 88%) (Scheme 6).[19]



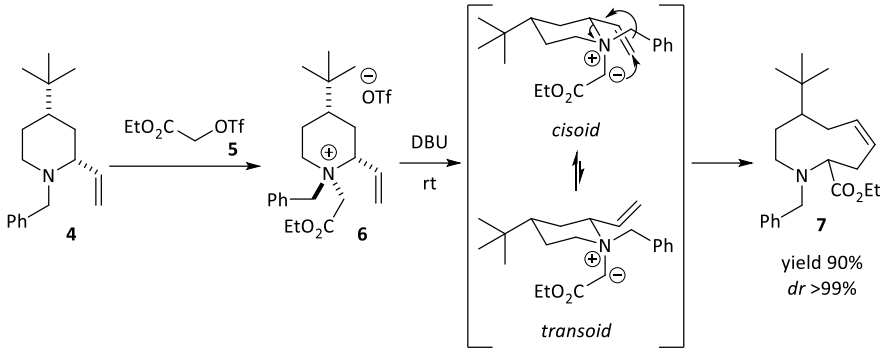
Scheme 6 *Synthesis of the optically active ketone* ***3***

In a [2,3]-sigmatropic rearrangement of ammonium ylides, a stereoselectively quaternised nitrogen can be used to determine stereoselective formation of the desired product (Scheme 7). The diastereoselective quaternisation of a starting material provides a temporary stereocentre on the nitrogen atom. Proton abstraction results in the formation of a corresponding ylide and the concomitant loss of the original stereocentre. Finally, the stereocentre is regenerated stereoselectively through the [2,3]-sigmatropic rearrangement due to chirality transfer from the nitrogen atom.[20]



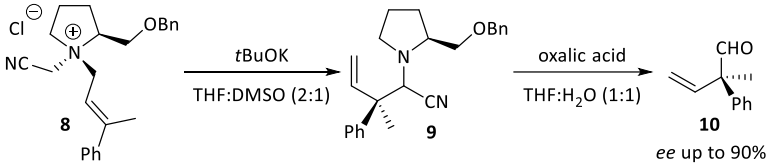
Scheme 7 *Carbon-nitrogen-carbon chirality transfer strategy*

In 1978, Vedejs *et al.* introduced a ring expansion method of the six-membered heterocycle **4**. After the diastereoselective quaternisation of 2-vinylpiperidine **4** with compound **5**, a DBU-mediated [2,3]-rearrangement was carried out. Due to the spatial closeness of the anion-stabilising group to the vinyl moiety, the reaction proceeded through the *cisoid*-transition state, providing excellent diastereoselectivity (*dr* >99%) of the nine-membered compound **7** (Scheme 8).[21] In addition, the [2,3]-sigmatropic rearrangement of similar five-membered *N*-heterocycles was also described by the same research group. Both *cis*- and *trans*-2-vinylpyrrolidinium salts, obtained via alkylation with compound **5**, were used, affording eight-membered products. However, due to the instability of the *trans*-product, only the *cis*-product was isolated in both cases.[22]



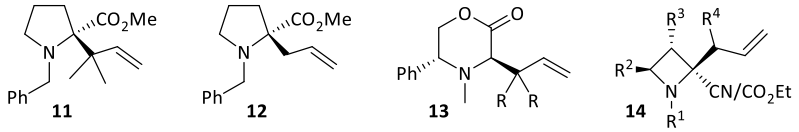
Scheme 8 *Rearrangement reaction of 2-vinylpiperidine* ***4***

Preparation of the optically active α,β-unsaturated aldehyde **10** was described by Hiroi *et al.* in 1980. After alkylation of the corresponding proline derivative with cyanomethyl chloride, enantiomerically enriched quaternary proline derivative **8** was obtained. Subsequent rearrangement in the presence of *t*BuOK provided aminonitrile **9**, which after hydrolysis with oxalic acid afforded aldehyde **10**. Depending on the rearrangement conditions, aldehydes were obtained with up to 90% of enantiomeric excess (Scheme 9).[23]



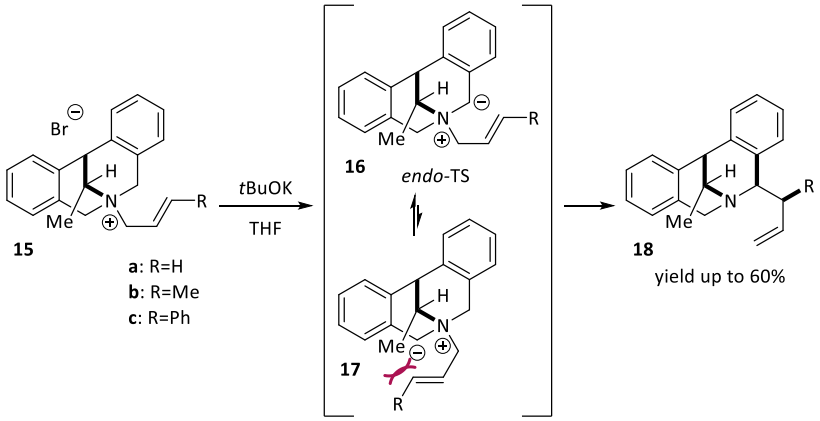
Scheme 9 *Synthesis of the optically active aldehyde* ***10***

West and co-workers utilised the same approach with other proline derivatives, as they envisioned that the rigidity of cyclic substrates would improve the chances of complete chirality transfer from nitrogen to carbon. Treatment with *tert*-butoxide of the prenyl bromide-alkylated ammonium salt yielded rearranged product **11** in excellent enantioselectivity.[24] Inspired by the investigation of the nitrogen-to-carbon chirality transfer reported by West *et al.*, other research groups started to broaden the scope of this type of self-regeneration of chirality. A year later, Coldham *et al.* published a simplified method for obtaining proline derivative **12** without the isolation of the ammonium salts. After diastereoselective quaternisation of the starting material with allyl iodide, *in situ* formed ylide spontaneously underwent [2,3]-sigmatropic rearrangement. Depending on the reaction conditions, product **12** was obtained with moderate yields (up to 48%) and good enantioselectivities (up to 86%).[25] In 2005, Tayama *et al.* introduced a diastereoselective pathway for the synthesis of the α-amino acid analogues **13** starting from morpholine derivatives.[26] Couty *et al.* further expanded the scope of cyclic products that can be obtained through [2,3]-rearrangement reaction utilising the C-to-N-to-C chirality transfer approach. A series of substituted azetidines **14** were prepared with diastereoselectivities up to 98:2 (Scheme 10).[27]



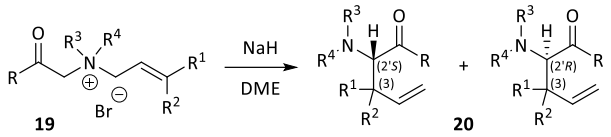
Scheme 10 *Additional examples based on carbon-nitrogen-carbon chirality transfer*

Isopavine is a well-known alkaloid that exhibits diverse pharmacological properties. In 2005, a base-catalysed [2,3]-sigmatropic rearrangement of the isopavine core containing polycyclic compounds **15** was reported by the Hanessian group. In the presence of a strong base, rearranged products **18** were obtained as single diastereomers with moderate yields (up to 60%). Additional experiments revealed that the deprotonation of the starting material occurred in a non-regioselective manner, leading to the formation of both ylides **16** and **17**. However as ylide **17** is more sterically restricted, equilibrium is shifted towards the formation of ylide **16**, thus providing the product via the preferred *endo*-transition state (Scheme 11).[28]



Scheme 11 *Rearrangement reaction of the polycyclic compounds* ***15***

In addition to methods that utilise already enantioenriched starting materials, the incorporation of a chiral auxiliary into the substrate for the rearrangement can be applied to provide a stereoselective reaction. In contrast to the examples described earlier, this method offers flexibility as the presence of a chiral auxiliary is temporary and it can be removed after the completion of the reaction. A successful implementation of this approach with the [2,3]-sigmatropic rearrangement of ammonium ylides was published by Sweeney *et al.* in 2004. Commonly employed camphorsultam was used as a chiral auxiliary providing a wide range of tertiary amines **20a-g** in a highly diastereoselective manner. It's noteworthy that in the case of substrates with $R^1 \neq R^2$ (**20e** and **20g**) excellent *anti*:*syn* selectivity was also achieved (>99:1) (Scheme 12, A). Moreover, there appeared to be no crucial difference in the position of the camphorsultam moiety in the substrate. This was confirmed by a rearrangement reaction performed with ammonium salt **19h**, where the auxiliary was transferred to the allylic substituent of the glycine derivative. As a result, excellent stereoinduction was also observed (Scheme 12, B).[29]



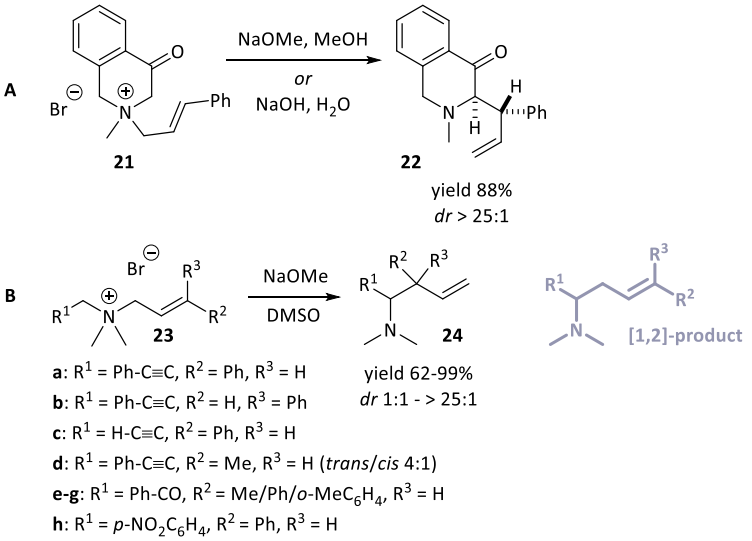
			a: R^1,R^2 = H, R^3,R^4 = Me **b**: R^1,R^2 = H, R^3 = Me, R^4 = allyl **c**: R^1,R^2 = H, R^3 = allyl, R^4 = allyl **d**: R^1,R^2 = H, R^3 = Bn, R^4 = allyl **e**: R^2 = H, R^1,R^3,R^4 = Me **f**: R^1,R^2,R^3,R^4 = Me **g**: R^1 = MeO_2C, R^2 = H, R^3,R^4 = Me
A	R = (*2R*)- or (*2S*)-camphorsultamyl	yield up to 99% if R was (*2R*) - (*2'S*) up to 98% if R was (*2S*) - (*2'R*) up to 99%	
B	R = OMe	yield 94% *ee* 96:4 ((*2'S,3'R*):(*2'R,3'S*)) *dr* 97:3 (*anti*:*cis*)	**h**: R^1 = C(O)-(*2S*)-camphorsultam, R^2 = H, R^3,R^4 = Me

Scheme 12 *Rearrangement reaction of the camphorsultam-containing ammonium salts* ***19***

1.1.2 Base-catalysed rearrangement originating from racemic/achiral ammonium salts

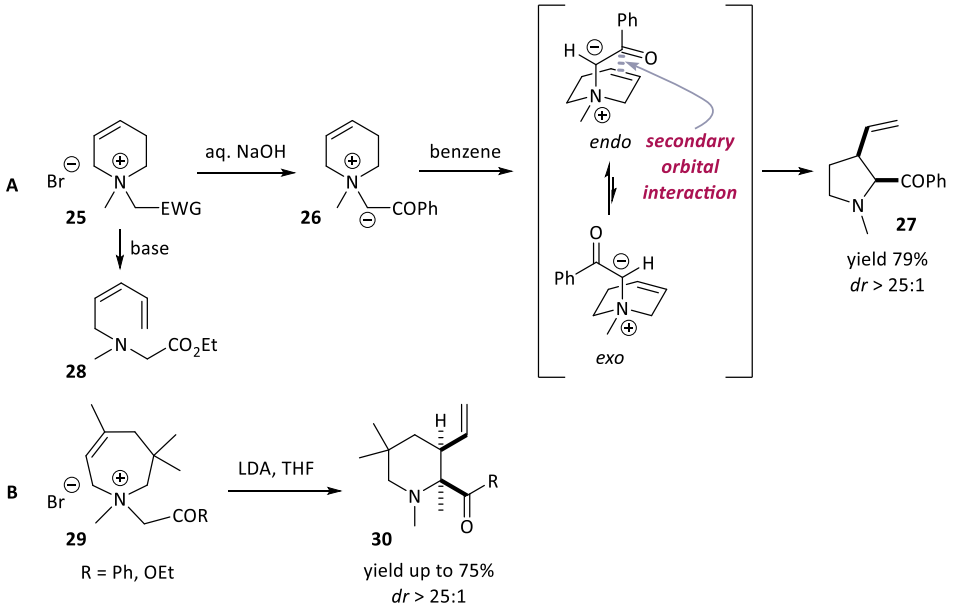
In addition to examples utilising already non-racemic starting materials, racemic/achiral ammonium salts have also been used in [2,3]-sigmatropic rearrangement reactions. In this case, substrate design is especially crucial, as steric effects play a significant role in influencing the diastereoselectivity of the reaction. The size of the substituents in the substrate directs the rearrangement either in an *endo*- or *exo*- transition state, leading to the predominant formation of one diastereomer.

The extensive work of Ollis *et al.* revealed many factors that can influence the rate and diastereoselectivity in this category. In general, due to rigidity, cyclic ammonium salts tend to rearrange with a high level of diastereocontrol. Thus, in the presence of NaOMe or NaOH, the diastereoselective rearrangement of *N*-heterocyclic ammonium salt **21** afforded compound **22** as a single diastereomer (Scheme 13, A).[30] In contrast, aliphatic acyclic ammonium salts **23** acted differently. The diastereoselectivity of the obtained products was highly dependent on the substituents of the starting material. For example, a rearrangement reaction with ammonium salt **23c** afforded a single diastereomer of product **24c** in excellent yield (99%). However, crotyl-substituted ammonium salt **23d** led to the formation of the respective product **24d** with a diastereomeric ratio of 1:1. Moreover, in some cases, the formation of the competitive [1,2]-Stevens rearrangement product was also observed. Ollis *et al.* believed that stabilisation of the formed ylide is one of the factors affecting the ratio of the [2,3]- and [1,2]-products. They also proposed that the bulkiness of the allyl substituents raises the energy barrier for a [2,3]-rearrangement reaction, thus causing an increase in the formation of the [1,2]-side product (Scheme 13, B).[31,32]



Scheme 13 *First examples of Ollis et al.'s work*

Later, the same research group introduced another example of a rearrangement reaction of cyclic 1,2,3,6-tetrahydropyridine ammonium salt **25** substituted with a ketone moiety as an electron-withdrawing group. Stable ylide **26** was isolated after the deprotonation of the starting material with NaOH, and further use of elevated temperatures in benzene provided *cis*-disubstituted pyrrolidine **27**.[33] Formation of the product in a high diastereomeric ratio was rationalised by the shifted equilibrium towards an *endo*-transition state that was favoured because of a secondary orbital interaction between the anion-stabilising carbonyl moiety and alkene.[34] To extend the synthetic utility of this reaction, Stevenson *et al.* continued investigation with a 1,2,3,6-tetrahydropyridine ammonium salt **25** bearing an ester group as the EWG. Surprisingly, only Hoffmann elimination product **28** was formed. Increased basicity and geometrical constraints of the used starting material were proposed as reasons for the observed results (Scheme 14, A). However, changing the ring size of the starting material from six- to seven-membered entirely excluded the elimination reaction pathway. Therefore, the LDA-catalysed ring contraction method of tetrahydroazepine derivatives **29** was established, providing *cis*-disubstituted piperidines **30** in good yields (Scheme 14, B).[35,36] Taking into account the preliminary results reported by the Stevenson group, Sweeney *et al.* provided a systematic study of the described findings. The obtained results revealed that, in the case of ammonium salts **25** with ester moieties as the EWG, NaH can be used instead of LDA to decrease the amount of elimination side product. Furthermore, the bulkiness and substitution pattern of the EWG drastically influenced the ratio of the desired rearranged product and undesired elimination product, which confirmed the significance of the steric demands and, thus, the involvement of the secondary orbital interaction in the transition state of the rearrangement reaction.[37]

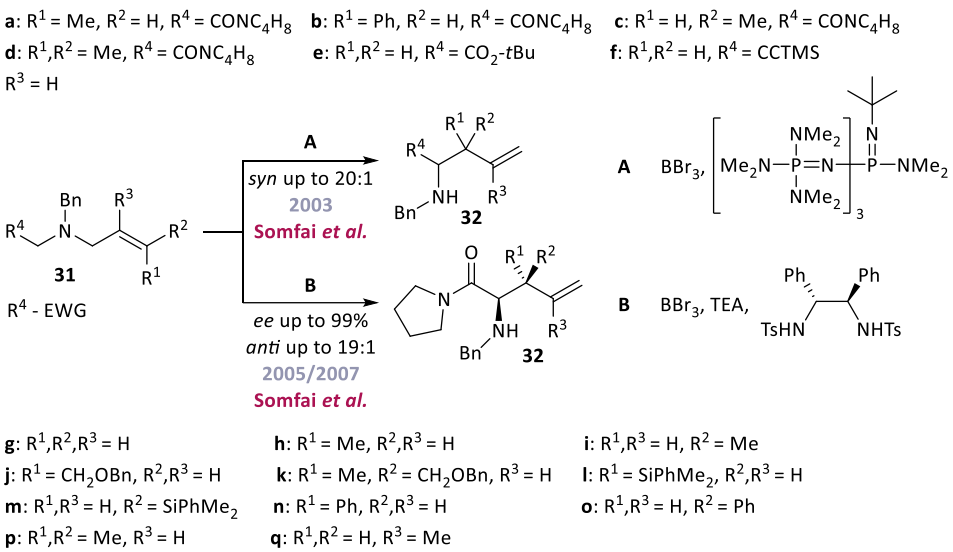


Scheme 14 *Differences in the [2,3]-sigmatropic rearrangement outcomes with six- and seven-membered rings*

1.1.3 Asymmetric [2,3]-sigmatropic rearrangement of ammonium ylides

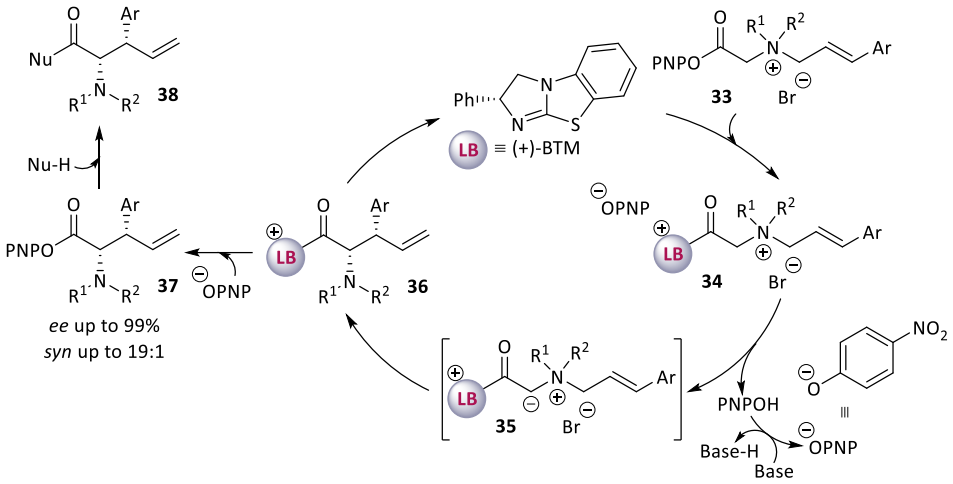
The most widely explored methods for the enantioselective construction of new stereogenic centres in a [2,3]-sigmatropic rearrangement of ammonium ylides utilise specific chiral metal-ligand combinations to selectively direct the formation of a metallocarbene intermediate.[38] Despite the significant progress made in the field of organocatalysis over the past few decades, achieving enantiocontrol in the [2,3]-sigmatropic rearrangement of ammonium ylides using organocatalytic systems still poses a challenge. This is mainly attributed to the reactivity of the ammonium ylides and the lack of coordination between the catalyst and substrate.[39]

In 2003, Somfai *et al.* introduced a notable method for the [2,3]-sigmatropic rearrangement of ammonium salts, which were generated via *in situ* complexation with a stoichiometric amount of Lewis acid, followed by deprotonation with a Schwesinger phosphazene base. After hydrolysis, corresponding secondary amines **32a-d** were obtained in 56 – 71% yields. Using pyrrolidinyl amide as an EWG (R^4) also led to the formation of products **32a-c** with excellent diastereoselectivities (up to 20:1) (Scheme 15, A).[40,41] Considering these findings, an enantioselective version was successfully developed by the same research group. Chiral Lewis acids based on boron complexes with C_2-symmetric sulfonamides were found to be very efficient, leading to the formation of secondary amines **32g-q** with excellent diastereo- and enantioselectivities. Moreover, additional optimisation revealed that milder reaction conditions could be used without a decelerating reaction; the previously used strong phosphazene base was replaced with triethylamine. Unfortunately, the described approach has some limitations as it required an excess of all other reagents: two equivalents of both sulfonamide and Lewis acid, as well as five equivalents of base had to be used to obtain the desired products (Scheme 15, B).[42,43]



Scheme 15 *Lewis acid-mediated rearrangement reaction of tertiary amines* ***31***

In 2014, Smith and co-workers reported an elegant and until now the only catalytic enantioselective method, which they followed up in 2017. The rearrangement reaction was conducted with either isolated or *in situ*-generated ammonium salts **33** using a chiral isothiourea as a catalyst. In the catalytic cycle, the first step included the replacement of the good phenolate-leaving group of the starting material by the Lewis base benzotetramisole ((+)-BTM), leading to the formation of crucial chiral intermediates **34**. The released *p*-nitrophenoxide (OPNP) acted as a base, creating corresponding ylides **35**, which underwent a sigmatropic rearrangement, leading to the formation of intermediates **36**. Catalyst turnover occurred via a nucleophilic substitution of intermediates **36** by the *p*-nitrophenoxide, which was regenerated in the presence of the additional base. Isolated *syn*-configured products **37** were obtained with excellent diastereo- and enantioselectivities. In addition, to show synthetic utility, *p*-nitrophenyl substituted products **37** were treated with different nucleophiles, providing a broad scope of α-amino acid derivatives **38** (Scheme 16).[44,45] Subsequently, Song *et al.* expanded the scope of this reaction to include propargyl ammonium salts. Employing the same methodology, they successfully synthesised highly functionalised allenes with excellent yields (up to 99%) and enantioselectivities (up to 96%).[46]

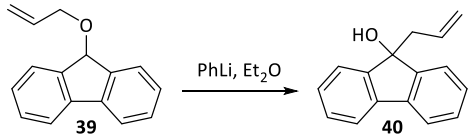


Scheme 16 *Catalytic cycle for the enantioselective synthesis of the α-amino acid derivatives* ***38***

1.2 [2,3]-Wittig rearrangement

The [2,3]-sigmatropic rearrangement of allyloxy-substituted carbanions represents a highly versatile methodology employed for the synthesis of homoallyl alcohols, allowing for the incorporation of up to two contiguous stereogenic centres.

In 1949, during the investigation of the isomerisation processes of fluorenyl ethers, Georg Wittig and colleagues discovered the unexpected product **40** formed via rearrangement of the (allyloxy)fluorene derivative **39** (Scheme 17).[47] Further investigation of the reaction mechanism revealed that, as in the case of the [2,3]-sigmatropic rearrangement of ylides, a competitive [1,2]-shift can occur depending on the nature of the chosen substrate and the reaction conditions.[48,49,50]



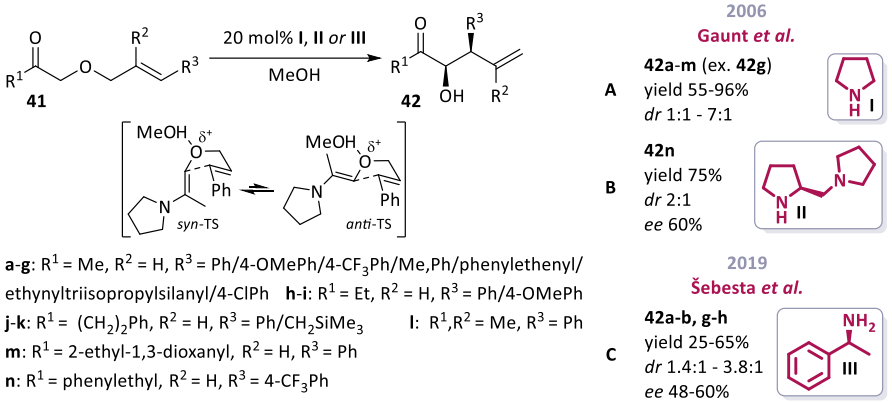
Scheme 17 *The first example of the [2,3]-Wittig rearrangement*

Nowadays, commonly known as the [2,3]-Wittig rearrangement, this subtype was selected as an example of anionic [2,3]-sigmatropic rearrangement reactions in the current study. The present chapter focuses on the organo- and metal-catalytic enantioselective version of the [2,3]-Wittig rearrangement, and therefore emphasis is deliberately placed on these catalytic approaches, omitting examples involving chirality transfer or the utilisation of stoichiometric reagents.

The initial examples of an asymmetric [2,3]-Wittig rearrangement reaction involving a chirality transfer from the starting material to the product were reported as early as 1971.[51] Subsequently, numerous valuable methodologies have been developed, covering the application of chiral auxiliaries, bases and the stoichiometric amounts of chiral catalysts and ligands[52,53,54], which have paved the way for the progression to catalytic methodologies.

1.2.1 Asymmetric organocatalytic [2,3]-Wittig rearrangement

The first organocatalytic [2,3]-Wittig rearrangement reaction was introduced by Gaunt *et al.* in 2006. Utilising a simple secondary amine pyrrolidine **I**, the diastereoselective rearrangement of acyclic ketones **41a**-**m** (ex. **41g**) was developed (Scheme 18, A). A protic solvent (in this case MeOH) was found to be essential for high diastereoselectivity. It was proposed that, in the catalytic cycle, during the formation of an enamine intermediate, additional hydrogen bonding between the solvent and the oxygen atom of the ether occurred. This led to the stabilisation of the formed negative charge. The reaction is believed to have proceeded favourably through the *syn* transition state (*syn*-TS), which led to formation of the *cis*-product. In addition, in the same article, the first example of an enantioselective organocatalytic asymmetric [2,3]-Wittig rearrangement was shown (Scheme 18, B). A replacement of an achiral pyrrolidine **I** with a chiral secondary amine **II** provided the rearranged product **42n** with moderate *dr* (2:1) and *ee* (60%).[55] Thirteen years later, Šebesta *et al.* reinvestigated the [2,3]-Wittig rearrangement of acyclic ketones. Despite the exhaustive examination of various primary and secondary amines in diverse solvent systems, their efforts to enhance the outcome resulted in no improvements, resulting in the formation of products **42a**-**b**, **g**-**h** with a maximum enantioselectivity of 60% (Scheme 18, C).[56]

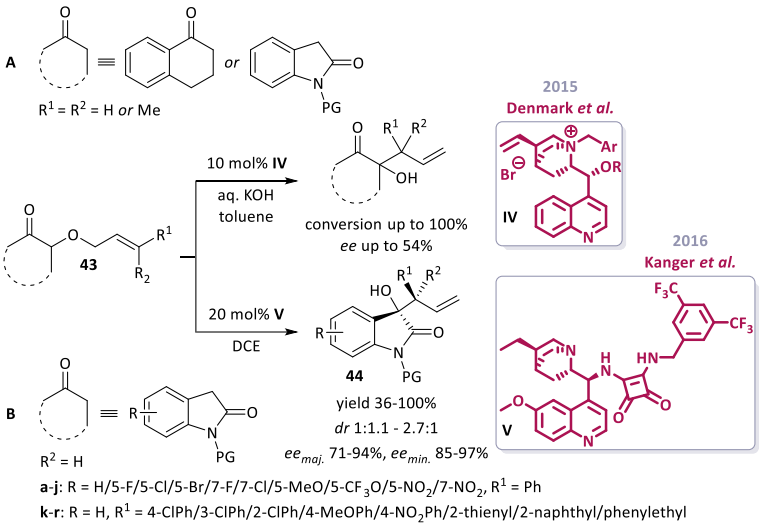


a-**g**: R^1 = Me, R^2 = H, R^3 = Ph/4-OMePh/4-CF_3Ph/Me,Ph/phenylethenyl/ethynyltriisopropylsilanyl/4-ClPh **h**-**i**: R^1 = Et, R^2 = H, R^3 = Ph/4-OMePh **j**-**k**: R^1 = $(CH_2)_2$Ph, R^2 = H, R^3 = Ph/CH_2SiMe_3 **l**: R^1,R^2 = Me, R^3 = Ph **m**: R^1 = 2-ethyl-1,3-dioxanyl, R^2 = H, R^3 = Ph **n**: R^1 = phenylethyl, R^2 = H, R^3 = 4-CF_3Ph

Scheme 18 *Primary or secondary amine-catalysed [2,3]-Wittig rearrangement of acyclic ketones* ***41a-n***

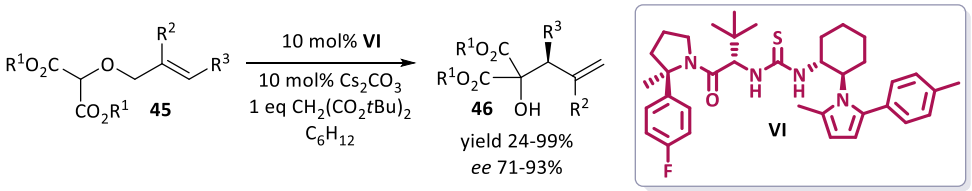
In 2015, increased research interest and development in the field of phase-transfer catalysis, prompted the Denmark group to investigate the [2,3]-Wittig rearrangement reaction under phase-transfer reaction conditions. In this thorough study, various chiral quaternary ammonium salts were systematically evaluated as catalysts while also exploring the impact of the bases on the rate and selectivity of the reaction. Despite extensive effort and enormous research volume, only moderate enantioselectivities (up to 54%) were achieved. Two factors were identified to elucidate such an outcome. It was shown that in the absence of the catalyst an undesired base-catalysed racemic background reaction could still occur. Moreover, the authors of the article proposed that stereodifferentiation depended on substituents of the allyloxy moiety. In the case of the chosen substrates, this led to a rather minor difference between transition state energies (Scheme 19, A).[57] Soon after, our research group presented the first asymmetric organocatalytic hydrogen bond-mediated [2,3]-Wittig rearrangement of oxindole derivatives. This methodology utilised *Cinchona* alkaloid-derived bifunctional

catalyst **V**, providing 3-hydroxy 3-substituted oxindoles **44** with high enantioselectivity. The diastereoselectivity of the reaction appeared to be moderate. However, this did not diminish the value of this approach, since the diastereomers were chromatographically separable. Notably, a π-π interaction between the allyloxy moiety of the substrate and the catalyst played an essential stabilising role in the transition state, as only starting materials containing the aromatic ring exhibited reactivity under the optimised conditions (Scheme 19, B).[58]



Scheme 19 *The phase-transfer-catalysed and hydrogen bond-mediated [2,3]-Wittig rearrangement of cyclic carbonyl allyloxy derivatives* ***43***

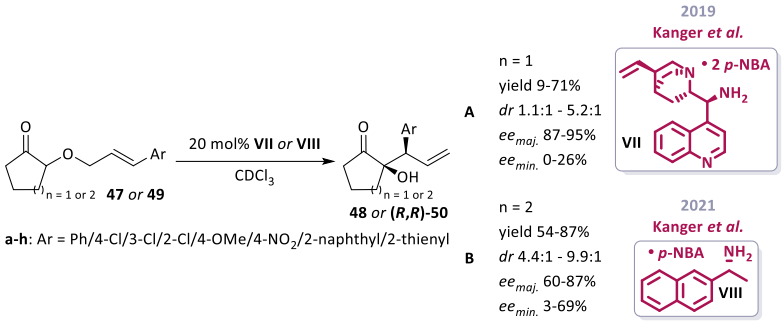
At the same time, Jacobsen *et al.* found a highly effective thiourea and Brønsted base co-catalysis. Systematic screening of the catalysts revealed that each part of the thiourea **VI** (arylpyrrole and 2-arylpyrrolidine substituents, as well as amide moiety) is essential to achieve high enantioselectivities (Scheme 20). Additionally, based on the DFT calculations, it was proposed that a non-covalent cooperative combination of both anion- and cation-binding motifs led to the stabilisation of the rearrangement transition state, therefore enhancing enantioselectivities of the products **46**.[59]



a-b: R^1 = Me, R^2 = H/Me, R^3 = Ph **c-d**: R^1 = Et, R^2 = H/Me, R^3 = Ph
e-t: R^1 = *t*Bu, R^2 = H/Me, R^3 = Me/CF_3/Ph/4-ClPh/3-ClPh/2-ClPh/4-FPh/ 4-CF_3Ph/4-MePh/4-MeOPh/2-naphthyl/1-naphthyl/2-thienyl/2-furyl/2-pyrrolyl

Scheme 20 *Thiourea-catalysed [2,3]-Wittig rearrangement of malonate derivatives* ***45***

Taking inspiration from Gaunt's research involving acyclic ketones, our research team introduced an enamine co-catalytic system in conjunction with an acidic additive in 2019. The *p*-NBA salt of the *Cinchona* alkaloid-derived primary amine **VII** provided α-branched cyclopentanones **48** with excellent enantioselectivities for the major diastereomer. Surprisingly, in all cases, the *ee* of the minor diastereomers appeared to be low. Furthermore, it was observed that the optimised reaction conditions were unsuitable for a cyclohexanone derivative, resulting in a substantial reduction in both yield and enantioselectivity (Scheme 21, A).[60] As a result, in 2021, our research group embarked on extending the application of the aforementioned method by incorporating slightly enlarged six-membered ketones **49**. Here, the *p*-NBA salt of the (2-naphthyl)ethylamine **VIII** was highly efficient, resulting in good yields, diastereoselectivities and enantioselectivities for the major diastereomer of α-hydroxyketones **(*R*,*R*)-50**. Unfortunately, similar to the scenario observed with cyclopentanone derivatives **47**, low enantioselectivities for the minor diastereomers were obtained. Subsequent reaction monitoring disclosed an inconsistency of the *ee* of both diastereomers throughout the reaction, with a pronounced decline observed over time, especially significantly for the minor diastereomer (Scheme 21, B).[61]

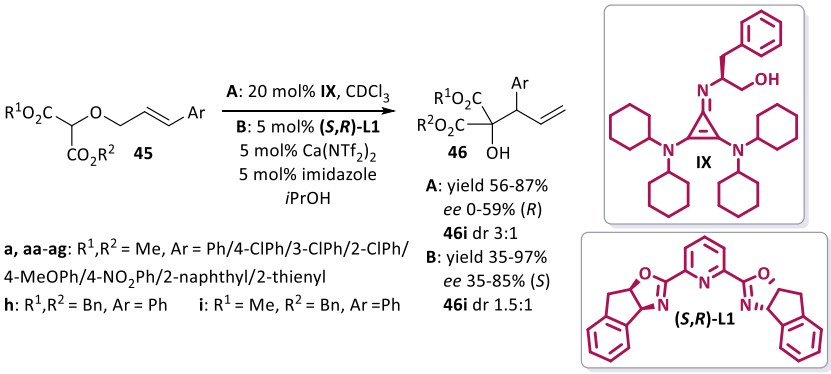


Scheme 21 *Primary amine-catalysed [2,3]-Wittig rearrangement of cyclic ketones **47** and **49***

1.2.2 Asymmetric metal-catalysed [2,3]-Wittig rearrangement

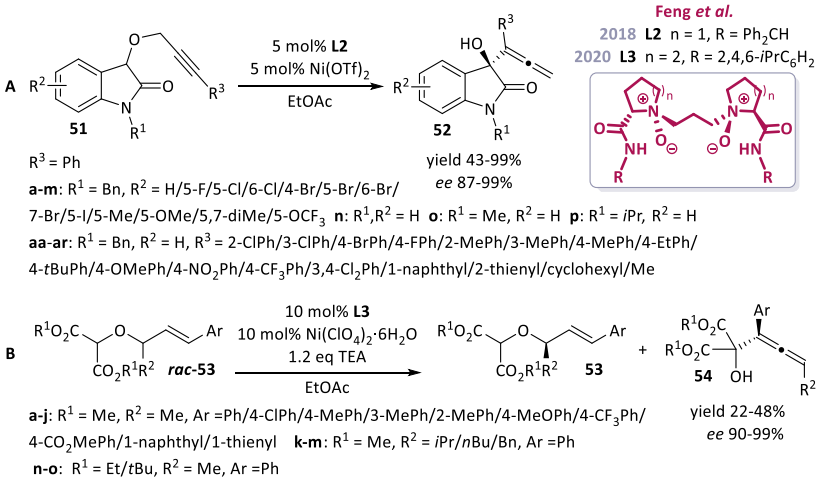
Some stoichiometric methods (*e.g.* Maezaki *et al.*[62]) and methodologies involving the generation of chiral Li-enolates[63,64] have been previously described. Nevertheless, only a few examples currently represent catalytic metal-catalysed [2,3]-Wittig rearrangements.

In 2017, our research group published our findings on a [2,3]-Wittig rearrangement of malonate derivatives. The initial screening of the organocatalytic protocol revealed that the implementation of the highly reactive catalyst **IX**, featuring a cyclopropenimine scaffold, facilitated the formation of rearranged products **46** with good yields (up to 87%) and moderate enantioselectivities (up to 59%) (Scheme 22, A). Notably, within the same publication, an alternative approach was introduced. Interestingly, when compared to the organocatalytic method, a combination of a calcium salt with a suitable ligand **(*S*,*R*)-L1** exhibited enhanced enantioselectivity in the rearrangement reaction, resulting in even higher yields (up to 97%) and enantioselectivities (up to 85%) in the formation of products **46** (Scheme 22, B).[65]



Scheme 22 *Chiral organic base- and calcium-based Lewis acid-catalysed [2,3]-Wittig rearrangement of malonate derivatives* ***45***

A year later, Feng *et al.* developed a highly effective method for the [2,3]-Wittig rearrangement of propargylic ethers **51**. This approach utilised a nickel salt in combination with chiral *N*,*N*-dioxide ligand **L2**. Despite the low reactivity of propargylic ethers, in almost all cases corresponding allenes **52** were formed in excellent yields (up to 99%) with very high enantioselectivities (up to 99%). Based on the X-ray analysis of the product, it was proposed that the *Re* face of the formed enolate is hindered by the bulky diphenylmethyl moiety of the ligand **L2**, therefore leaving the *Si* face open for an attack by the propargylic unit (Scheme 23, A).[66] In the aforementioned article, a noteworthy observation emerged in the case of the 4-phenylbut-3-yn-2-ol-derived racemic substrate, indicating the possibility of achieving kinetic resolution with the developed catalytic system. Further investigation in this field led to a subsequent publication in 2020. The optimised nickel-derived Lewis acid **L3** catalytic system demonstrated exceptional proficiency in the chiral recognition of one enantiomer of the starting material followed by chirality transfer in the [2,3]-Wittig rearrangement. As a result, variously substituted chiral α-hydroxyallenes were successfully synthesised from racemic malonate derivatives ***rac*-53**, exhibiting outstanding enantioselectivities of up to 99% (Scheme 23, B).[67]



Scheme 23 *Examples of nickel-ligand-catalysed [2,3]-Wittig rearrangement*

2 Aims of the present work

The provided literature overview highlights the significant advancements made in the field of [2,3]-sigmatropic rearrangement. Nevertheless, sustainability problems have now emerged as crucial concerns, requiring further investigation in pursuit of progress. In this regard, [2,3]-sigmatropic rearrangement reactions hold particular promise due to their inherent 100% atom efficiency and the opportunity to selectively generate up to two stereogenic centres simultaneously. Consequently, the primary focus of this work is to enhance the efficiency of [2,3]-sigmatropic rearrangement reactions, thereby fostering a more sustainable and resource-efficient approach to chemical synthesis.

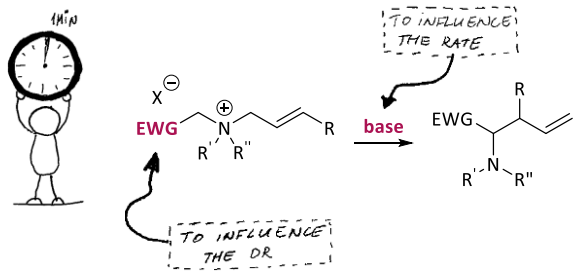
The specific aims of the thesis are:

- to develop an efficient method for the [2,3]-sigmatropic rearrangement reaction of *N*-allyl ammonium ylides;
- to examine the compatibility of enzymatic catalysis with metal- and organocatalysis;
- to elaborate a synthetic pathway for increasing the structural complexity of the [2,3]-Wittig rearrangement products containing prochiral malonate derivatives;
- to design a recyclable catalytic system for the asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives;
- to explore the viability of the designed catalysts under the [2,3]-Wittig rearrangement reaction conditions.

3 Results and discussion

3.1 Diastereoselective [2,3]-sigmatropic rearrangement of *N*-allyl ammonium ylides (Publication I and unpublished results)

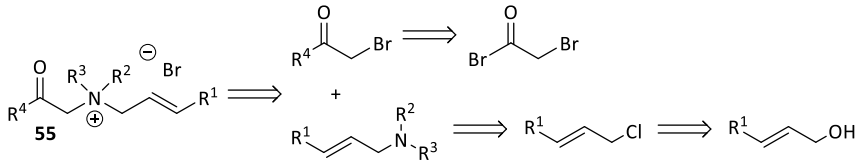
"Time is our most valuable asset, …" one of the pioneers of personal development, Jim Rohn, once said. This is true not only at the individual level but also for the successful and optimal functioning of businesses and industrial processes. Wise time management and efficient energy consumption are paramount considerations in achieving business success and optimising overall industrial operations. Considering the aforementioned concerns, along with our prior expertise in the field of rearrangement reactions and the absence of a systematic study regarding the diastereoselective [2,3]-sigmatropic rearrangement of *N*-allyl ammonium ylides, we devised a strategy aimed at discovering a rapid method for this transformation. We envisioned accelerating the reaction by influencing the deprotonation step and the diastereoselective outcome with an electron-withdrawing group of the starting material, as the steric properties and electronic effects of the EWG could affect the formation of the product by stabilising one of the transition states (Scheme 24).



Scheme 24 *General concept for the [2,3]-sigmatropic rearrangement of N-allyl ammonium ylides*

3.1.1 Synthesis of ammonium salts

In this study, the [2,3]-sigmatropic rearrangement was investigated by employing quaternary ammonium salts with different EWG moieties, along with variations in substituents on the nitrogen atom and allyl group. The majority of the starting materials for the rearrangement reactions were obtained through the quaternisation of tertiary amines with alkyl bromides. These alkyl bromides were, in turn, synthesised via the nucleophilic addition of nitrogen compounds (R^4 substituent) to bromoacetyl bromide. The preparation of tertiary amines involved the alkylation of the corresponding primary or secondary amines. Allyl chlorides were employed as alkylating agents in this process and were synthesised from alcohols when required (Scheme 25). Some variations in the synthetic pathway were made in the case of ammonium salts **55a**, **c** and **f**.



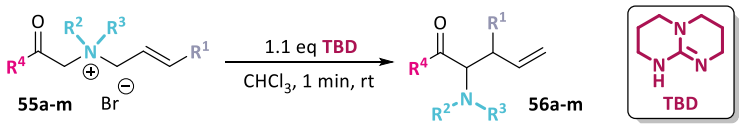
Scheme 25 *Retrosynthetic analysis for the synthesis of ammonium salts* ***55***

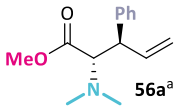
3.1.2 Diastereoselective [2,3]-sigmatropic rearrangement of ammonium salts

Next, we focused on the development of a diastereoselective approach for the [2,3]-sigmatropic rearrangement of ammonium salts **55**. Before surveying different bases and solvents suitable for the reaction, it was essential to identify an appropriate EWG group. Based on the preliminary results, the ammonium salt **55b** bearing oxazolidinyl group appeared to be the most efficient in terms of both reactivity and selectivity. Consequently, further optimisation was conducted utilising corresponding ammonium salt **55b**.

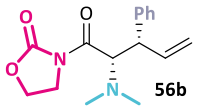
A screening of both organic and inorganic bases was performed for this reaction. As anticipated, the organic bases strongly influenced the reaction rate depending on their basicity. A strong correlation between the *p*Ka values and the reaction outcomes was observed. In sum, compared to the reactions with organic bases, experiments conducted with inorganic bases yielded more sluggish results; complete conversion was not reached, with diminished diastereoselectivity of the obtained product. Thus, guanidine-derived TBD emerged as an optimal base for the reaction, leading to complete conversion in only one minute while affording an excellent diastereoselectivity of 12.5:1. In addition, chloroform, initially selected as the solvent, remained the optimal choice, as even after further screening of alternative solvents, no improvement in the results was observed.

Next, the scope of the reaction was investigated. The results revealed that the diastereoselectivity of the [2,3]-sigmatropic rearrangement reaction significantly depends on the starting material's structural properties. Employing an oxazolidinyl group as an electron-withdrawing group led to good to excellent diastereoselectivity. However, other electron-accepting groups resulted in either inferior diastereoselectivity (*e.g.* as observed with the methyl ester-containing ammonium salt **55a**) or no reaction at all (*e.g.* as seen with the amide group-containing substrate **55d**). Moreover, the substituent on the allyl group influenced the course of the rearrangement reaction. The cinnamyl-substituted ammonium salt **55b** provided the rearrangement product **56b** with high diastereoselectivity. In contrast, the methyl-substituted **55g** afforded the product with *dr* 1.3:1. Apart from diastereoselectivity, the stability of the starting material was also impacted by the allyl substituent. Replacing the phenyl group with a methyl group or a hydrogen atom resulted in obtaining rearrangement products **56g** and **56h** only under dry conditions and with reduced yields due to degradation of the starting material. This occurrence can be explained by the phenyl group's interaction with the carbonyl group, inhibiting water addition to the latter. In cases where the allyl group has a different substituent than the phenyl group, the aforementioned interaction does not occur, allowing water to add to the starting material and, therefore, forming the corresponding acid and oxazolidinone. Furthermore, the diastereoselectivity of the reaction was also influenced by alkyl substituents on the quaternary nitrogen atom. Nonetheless, the formation of the corresponding products **56e** and **56f** occurred within 1 minute (Scheme 26).

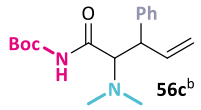




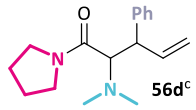
Yield 75%, *syn*:*anti* 1:1.5



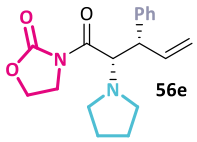
From ***trans*-55b**:
Yield 95%, *syn*:*anti* 13.3:1
From ***cis*-55b**:
Yield 95%, *syn*:*anti* 15.7:1



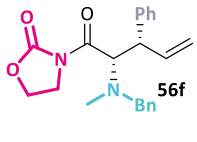
Yield 80%, *syn*:*anti* 1:1



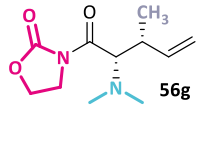
not formed



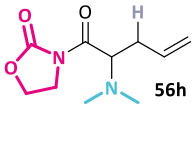
Yield 86%, *syn*:*anti* 10.1:1



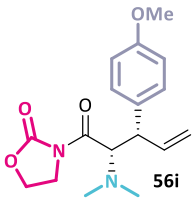
Yield 74%, *syn*:*anti* 7.3:1



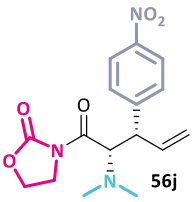
From ***trans*-55g**:
Yield 61%, *syn*:*anti* 1.3:1[d]
From ***cis*-55g**:
Yield 52%, *syn*:*anti* 1.3:1[d]



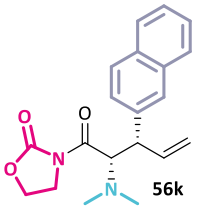
Yield 80%[d,e]



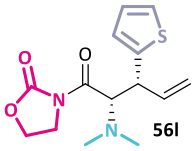
Yield 68%, *syn*:*anti* 8.1:1



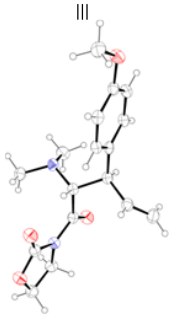
Yield 90%, *syn*:*anti* 6.1:1

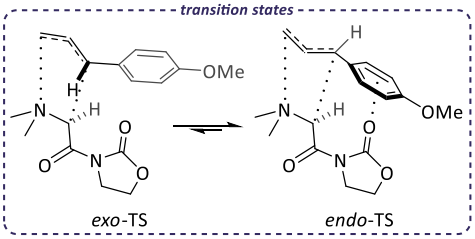


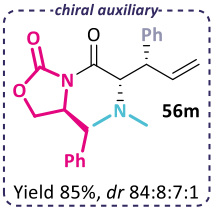
Yield 87%, *syn*:*anti* 10.1:1



Yield 83%, *syn*:*anti* 6.1:1







Yield 85%, *dr* 84:8:7:1

Reaction conditions: **55a-l** (1 eq), TBD (1.1 eq), $CHCl_3$ (0.25 M), rt, 1 min, stirring; isolated yields after column chromatography. The major diastereomer is depicted in the scheme. The *dr* was determined by ^1H NMR of the crude product. [a] Starting with the iodide salt of **55a**. [b] TBD (2 eq), stirring, 30 min. [c] 60 °C, 24 h. [d] Under Ar atmosphere with added molecular sieves (4 Å). [e] The purity of the product was 94%. The main impurity was oxazolidin-2-one, which has the same *Rf* value as compound **56h**.

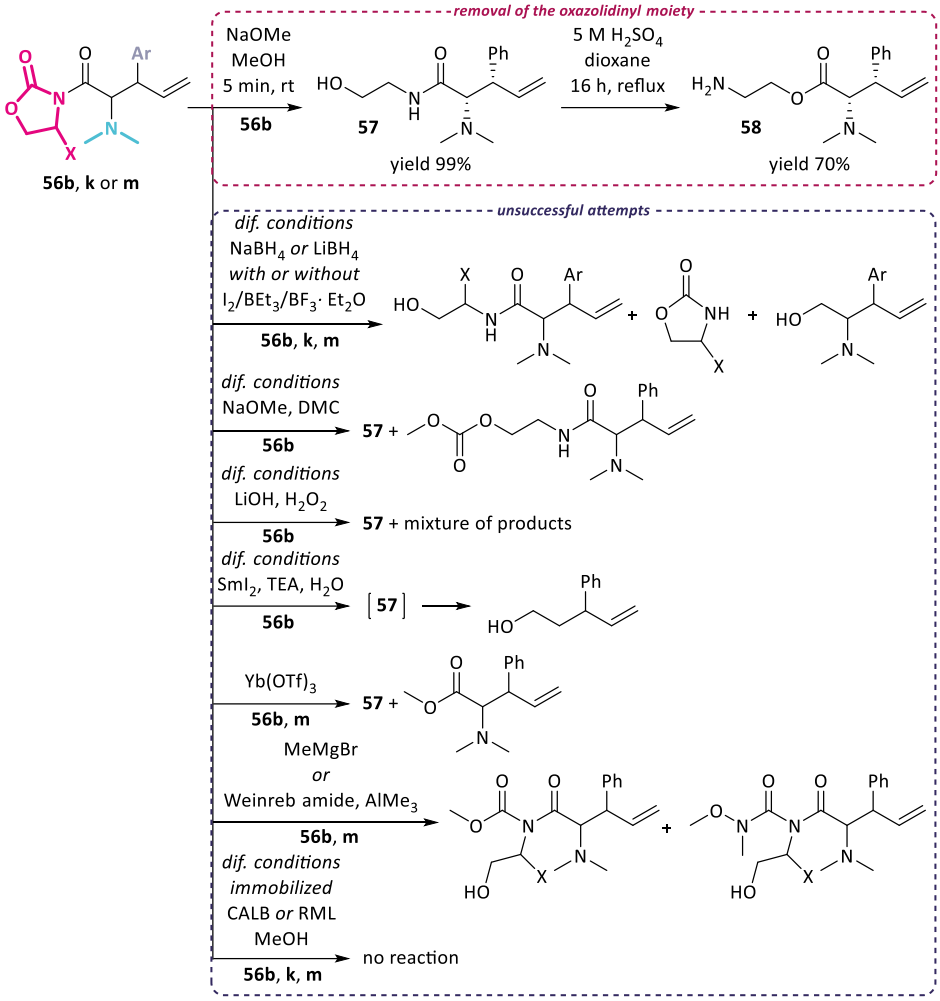
Scheme 26 *Scope of the [2,3]-sigmatropic rearrangement of ammonium salts* ***55***

Considering the crystal structure obtained for product **56i**, which showed the formation of the *syn*-product, a preference for the *endo* transition state was revealed. This can be rationalised by the presence of an additional stabilisation between the carbonyl group on the oxazolidinyl ring and the phenyl substituent of the allylic moiety. These findings correlated with the obtained experimental results, which emphasised the importance of the concurrent presence of both components (Scheme 26, *transition states*).

In addition to providing excellent diastereoselective control over the reaction, the employed oxazolidinyl moiety offers the advantage of facile substitution with its chiral analogue (Evans auxiliary), allowing for the introduction of enantioselectivity. Thus, utilising (*S*)-4-benzyloxazolidin-2-yl as an EWG under the optimised reaction conditions, the product **56m** was obtained with a *dr* of 84:8:7:1. Unfortunately, the formed diastereomers were inseparable, making it possible only to estimate that the rearranged product was formed with an *ee* of at least 83% (corresponding diastereomeric ratio of 84:8, Scheme 26, *chiral auxiliary*).

3.1.3 Removal of the oxazolidinyl moiety

To demonstrate the synthetic utility of the developed method, the removal of the oxazolidinyl moiety was attempted. Products **55** of the [2,3]-sigmatropic rearrangement of ammonium ylides primarily contain two competitive electrophilic carbonyl moieties. Two potential products can be formed depending on the site of the oxazolidinyl group removing reaction. The first is the endocyclic product, which arises from a reaction occurring within the oxazolidinone ring. The second is the exocyclic product, the focus of our interest, resulting from a reaction involving the carbonyl group outside the oxazolidinone moiety. Despite employing various methods with numerous variations to achieve this goal, all attempts resulted in the formation of the endocyclic cleavage product and a significant number of side-products, depending on the specific reaction conditions utilised.[68] Enzymatic hydrolysis was also attempted, but unfortunately, it yielded no positive outcome. By employing NaOMe in methanol, we directed the reaction towards the exclusive formation of endocyclic product **57**, achieving quantitative yields. Subsequently, relatively harsh hydrolytic conditions facilitated an intramolecular N-O acyl shift, leading to the formation of amino ester **58** in a 70% yield (Scheme 27).



Scheme 27 *Removal attempts of the oxazolidinyl moiety from the rearranged products*

3.1.4 Enantioselective [2,3]-sigmatropic rearrangement of ammonium salts

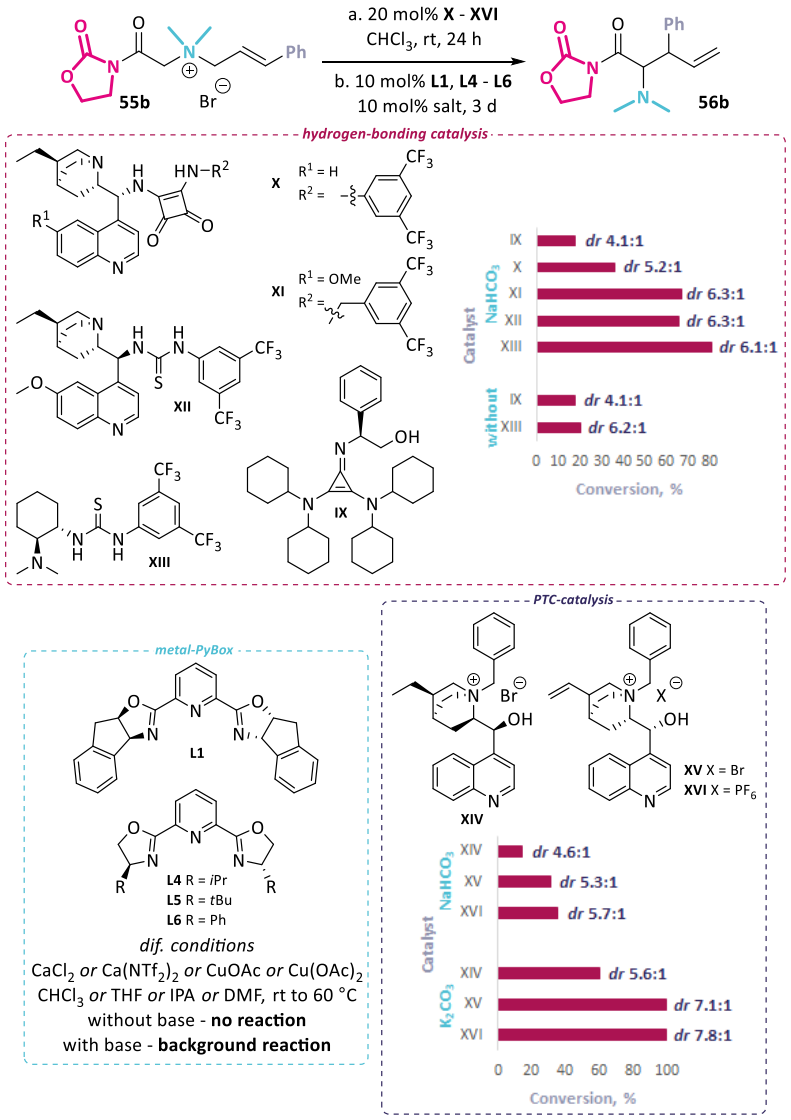
After successfully developing a diastereoselective method, our research aimed to explore a catalytic enantioselective system for the [2,3]-sigmatropic rearrangement reaction. To achieve this, we investigated various catalytic approaches, including hydrogen-bonding and phase-transfer catalysis, as well as a ligand-salt-based strategy. The starting material for our experiments was ammonium salt **55b**, chosen due to its previously demonstrated excellent performance in the diastereoselective [2,3]-rearrangement reaction.

For the series of the hydrogen-bonding catalysts, $NaHCO_3$ was selected as an additional base as it showed sluggish results in previous optimisation experiments of the diastereoselective [2,3]-rearrangement reaction, and thus the background reaction should have been diminished. The reaction involving cyclopropene imine **IX** as a catalyst exhibited 18% conversion after one hour, which remained constant after 24 hours. Despite a diastereomeric ratio of 4.1:1 in the resulting product, it was observed to be racemic. Subsequently, reactions were conducted with two squaramide-based catalysts

X and **XI**, Soos' catalyst **XII** and Takemoto's catalyst **XIII**. The catalysts influenced the reaction rate, yielding varying conversions. Notably, all reactions displayed generally high diastereoselectivities, while the resulting products were racemic. Considering this, additional control experiments were performed without a base to assess the impact of background reactivity. Using both Lambert's catalyst **IX** and Takemoto's catalyst **XIII** resulted in conversions up to the quantity of the used catalyst, yet the obtained products were racemic.

Regarding phase-transfer catalysis, *Cinchonidine*-derived catalysts **XV** and **XVI** exhibited slightly better conversions than *Cinchonine*-derived catalyst **XIV**. The reaction exhibited noticeable acceleration when a stronger base (K_2CO_3) was employed, surprisingly resulting in higher diastereoselectivities than when using the weaker $NaHCO_3$. Nevertheless, what holds greater significance was the absence of enantioselective induction in either case.

PyBox-derived ligands were also utilised in the investigated rearrangement reaction due to their well-established suitability for forming a complex with 1,3-dicarbonyl compounds in the presence of metal salts. Furthermore, we hypothesised the occurrence of additional ionic interactions between the catalytic system and the substrate. However, despite extensive exploration involving various combinations of Ca- and Cu-salts in different solvents, both at room temperature and elevated temperatures, the formation of the rearranged product was not observed. Moreover, introducing additional bases resulted in conversions corresponding solely to background reactions (Scheme 28).

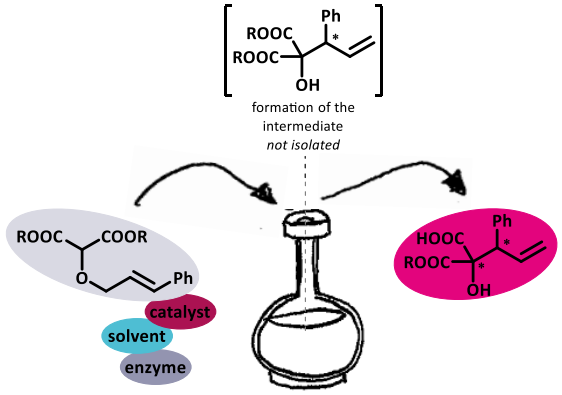


Scheme 28 *Exploration of enantioselective strategies in [2,3]-sigmatropic rearrangement reaction of ammonium ylides*

3.2 Asymmetric chemoenzymatic one-pot synthesis of α-hydroxy half-esters (Publication II and unpublished results)

Waste production is an inherent aspect of various processes, making complete elimination unfeasible. Nonetheless, it is possible to innovate and enhance efficiency in existing procedures or develop novel, more efficient ones. It is crucial to adhere to the atom-efficiency principle to enhance chemical processes. In addition, it is important to manage the formation of the by-product and eliminate unnecessary isolation steps whenever possible. Minimising the amounts of utilised chemicals is pivotal to generate less waste. Implementing catalytic systems instead of stoichiometric ones can yield notable benefits as, in this case, the amount of the used reagents was significantly

decreased. Furthermore, employing chemicals from renewable sources amplifies these advantages. As a result, our next endeavour focused on integrating the described principles for the synthesis of structurally complex α-hydroxy half-esters by developing an asymmetric chemoenzymatic one-pot system. We envisioned demonstrating that a Ca^{2+}-catalytic system, along with pig liver esterase (PLE), would be compatible and suitable for this one-pot operation. Both systems can be considered renewable sources. Calcium, being non-toxic and one of the most abundant elements in Earth's crust,[69] qualifies as an ideal chemical candidate. PLE is an inexpensive and extensively employed enzyme for the asymmetric desymmetrisation of esters. The production of a crude mixture of isoenzymes of PLE involves only a few steps, including the extraction of the enzyme from porcine liver and subsequent lyophilisation of the obtained extract.[70] Therefore, implementing these two approaches in pursuit of our goal would be a small step towards promoting sustainability. To this end, we utilised the findings from our previous study on the [2,3]-Wittig rearrangement reaction of malonic derivatives[65] as the starting point for further optimising its combination with enzymatic hydrolysis. Notably, intermediate isolation was avoided, leading to the successful synthesis of α-hydroxy half-esters bearing two contiguous quaternary and tertiary stereocentres (Scheme 29).



Scheme 29 *General concept for the asymmetric chemoenzymatic one-pot synthesis of α-hydroxy half-esters*

PLE is a representative of the hydrolase family. These enzymes were deemed optimal for the biotransformation step as they exhibit a notable capability of catalysing the hydrolysis of both ester and amide bonds. Depending on the precise reaction conditions, they can also perform the reverse reaction, facilitating the formation of ester and amide bonds. Remarkably, this enzyme family is one of the most widely employed enzymatic catalytic systems in organic synthesis, for several reasons. Firstly, their ready commercial availability and low cost render them a pragmatic choice. Secondly, reactions involving hydrolases generally occur under reasonably mild conditions, minimising the need for harsh or extreme parameters. Additionally, hydrolases demonstrate remarkable selectivity. Furthermore, their inherent stability, which extends to their functionality even in the presence of organic co-solvents, further emphasises their utility. Their independence from additional co-factors also facilitates their appeal as biocatalysts, enhancing the feasibility of their integration into various synthetic processes.[71]

3.2.1 Preliminary study

Before investigating the integration of diverse complex systems in a one-pot manner, we aimed to attain a comprehensive understanding of enzymatic hydrolysis with our system. To achieve that, the following studies were conducted:

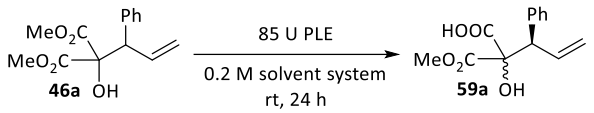
Supplementary study 1: Enzymatic hydrolysis with isolated racemic [2,3]-Wittig rearrangement product

This study started with optimising enzymatic hydrolysis, utilising isolated racemic [2,3]-Wittig rearrangement product. This study was essential due to the multiple parameters that can influence enzyme performance, including buffer type and pH, additives, and temperature. The initial step involved identifying an enzyme that would effectively hydrolyse the sterically demanding rearrangement product. Among different hydrolases screened, PLE demonstrated moderate but promising activity, making it the preferred enzyme for subsequent study. Additional experiments were conducted to determine the optimal enzyme loading, which appeared to be 85 units of enzyme per milligram of starting material (U). Unfortunately, extensive optimisation of various combinations of buffers with numerous additives did not yield satisfactory results. Nevertheless, this investigation not only revealed solvent systems, additives and their ratios that were unsuitable for enzymatic hydrolysis and, thus, helped us to avoid screening these in the more complicated one-pot reaction, but also identified promising solvent systems, such as a phosphate buffer (pH 8.0) with 20% DMSO and a Tris buffer (pH 8.5) with 20% $CHCl_3$, which were subsequently employed in further research.

Supplementary study 2: Enzymatic hydrolysis with isolated enantioenriched [2,3]-Wittig rearrangement product

We continued our investigation with enantioenriched [2,3]-Wittig rearrangement product to explore its potential to enhance enantioselectivities in enzymatic hydrolysis. Utilising the organocatalytic approach from our previous study (Scheme 22, A), the (*R*)-enantioenriched isomer of the rearrangement product was synthesised with an enantiomeric excess of 50%. Subsequently, employing the Ca^{2+}-ligand system (Scheme 22, B), the (*S*)-enantioenriched isomer was obtained with an *ee* of 72%. Next, the influence of buffers and additives on the hydrolysis of (*R*)-enantioenriched isomer was studied (presented in Table 1). In all cases, significantly higher diastereoselectivities were observed with excellent enantioselectivity of the minor diastereomer (except for the Tris buffer (pH 8.4)/$CHCl_3$ (8:2, 0.2 M), where the *ee* was lower). Generally, a higher pH value of the buffer facilitated a faster reaction, and the addition of DMSO increased the enantioselectivities of the major diastereomers, while decelerating the reaction. Moreover, the phosphate buffer demonstrated a positive influence on the reaction, leading to higher enantioselectivities than the Tris buffer. $CHCl_3$ as an additive did not provide any benefits compared to DMSO. To ascertain whether the opposite (*S*)-enantioenriched isomer influenced the reaction outcomes, hydrolysis in the phosphate buffer (pH 8.0)/DMSO (8:2, 0.2 M), which demonstrated an optimal conversion-to-*ee* ratio for the (*R*)-enantioenriched isomer, was performed (Table 1, entry 10). A substantial decrease in diastereoselectivity was observed, with very low enantioselectivity of the major diastereomer starting from the (*S*)-enantioenriched isomer. These findings confirmed the enzyme's clear preference for the (*R*)-enantioenriched isomer, prompting its use in subsequent experiments.

Table 1 *Influence of the enantioenriched [2,3]-Wittig rearrangement product on the hydrolysis*



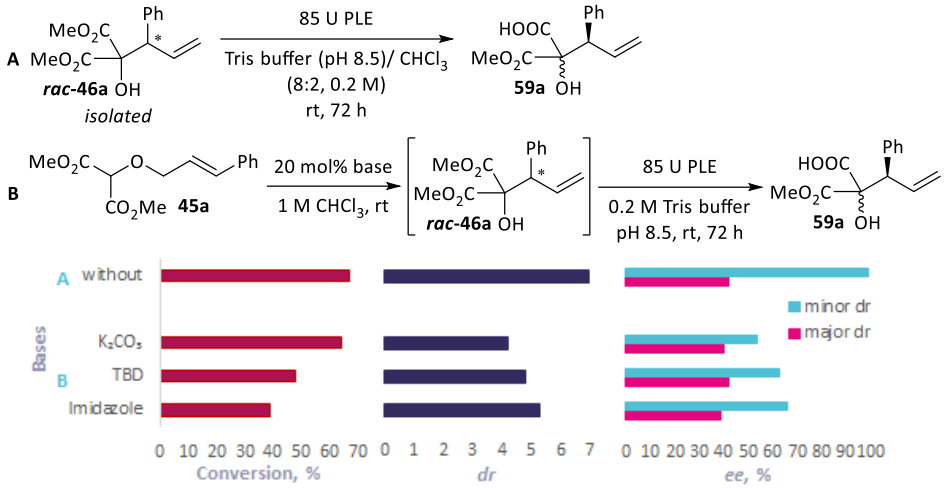
(***R***) *ee* 50% *or* (***S***) *ee* 72%

Entry	Isomer	Solvent system	Conv., %[a]	*dr*[b]	*ee*, %[c]	
					major dr	minor dr
1	(*R*)	TB (pH 8.5)	89	20:1	57	99
2	(*R*)	TB (pH 8.5)/$CHCl_3$ (8:2)	36	13:1	73	76
3	(*R*)	TB (pH 8.5)/DMSO (8:2)	47	14:1	69	99
4	(*R*)	PB (pH 7.5)	43	25:1	80	nd
5	(*R*)	PB (pH 7.5)/$CHCl_3$ (8:2)	18	19:1	83	99
6	(*R*)	PB (pH 7.5)/DMSO (8:2)	35	16:1	89	99
7	(*R*)	PB (pH 8.0)	81	15:1	68	99
8	(*R*)	PB (pH 8.0)/$CHCl_3$ (8:2)	35	16:1	77	99
9	(*R*)	PB (pH 8.0)/DMSO (8:2)	64	14:1	79	99
10	(*S*)	PB (pH 8.0)/DMSO (8:2)	58	2:1	-11	99

Reaction conditions: **(*R*)-** or **(*S*)-46a** (0.1 mmol), PLE (85 U), solvent system (0.2 M), rt, 24 h, vigorous stirring. [a] The conversion was determined by ^{1}H NMR of the crude mixture and referred to the ratio of the starting material and the product. [b] The *dr* was determined by ^{1}H NMR of the crude product. [c] The *ee* was determined by the chiral HPLC analysis of the sample obtained by preparative TLC; TB – Tris buffer, PB – phosphate buffer.

Supplementary study 3: The influence of bases on PLE-mediated desymmetrisation

Additionally, we investigated the possibility of combining a base-catalysed [2,3]-Wittig rearrangement reaction with hydrolysis. The hydrolysis results obtained with isolated racemic rearranged product ***rac*-46a** conducted in a Tris buffer (pH 8.4)/$CHCl_3$ (8:2, 0.2 M) solvent system was employed as a comparative benchmark (Scheme 30, A). Three different bases – TBD, imidazole and K_2CO_3 – were studied to assess their influence on the reaction. Chloroform was used in such an amount that the final buffer-cosolvent ratio in the hydrolysis step was 4:1. Once full conversion of the first step was achieved, an enzyme solution in the buffer was added (Scheme 30, B). The presence of both organic bases resulted in a deceleration of the reaction, while K_2CO_3 had no effect on the reaction rate. However, in all cases, diminished diastereoselectivities were obtained. Interestingly, all of the bases exhibited similar pattern, significantly reducing the enantioselectivities of the minor diastereomers while leaving the *ee* of the major diastereomers unaffected. Despite preserving the enantiomeric excesses in the major diastereomers, the overall results indicated a decline in enzyme activity in the presence of bases. Consequently, we decided not to pursue this topic further.

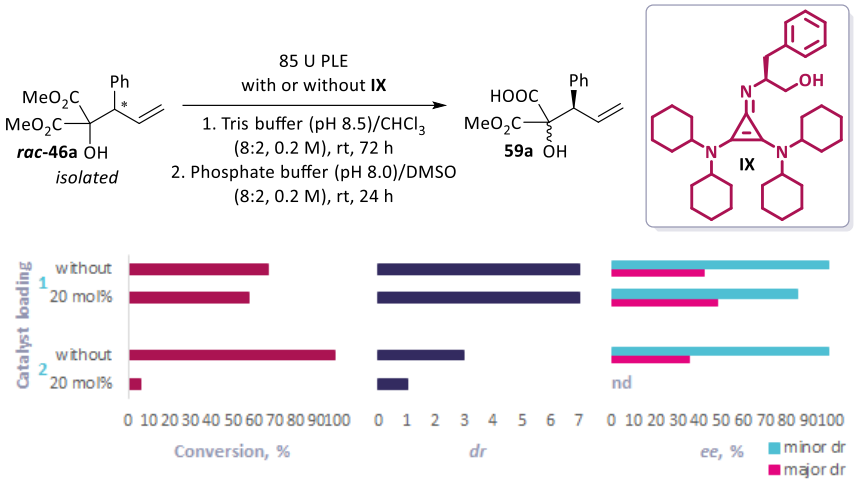


Scheme 30 *The influence of bases on PLE-mediated desymmetrisation in a one-pot reaction; the diastereoselectivity represents a ratio of X:1*

3.2.2 Implementation of organocatalytic [2,3]-Wittig rearrangement/PLE-mediated desymmetrisation in a one-pot reaction

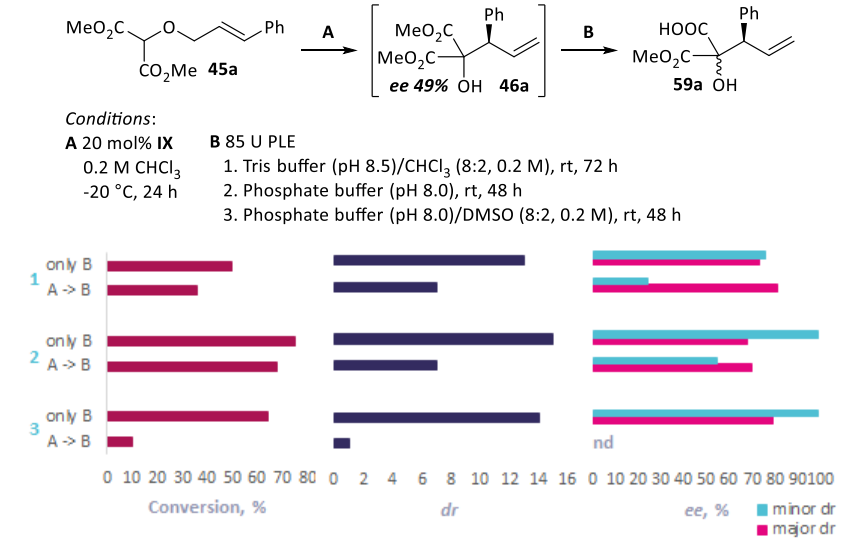
In our research group's publication on the [2,3]-Wittig rearrangement of malonic derivatives[65], which served as the basis for this study, two independent catalytic approaches were introduced (Scheme 22). However, no previous information was available regarding their influence on PLE-mediated hydrolysis. As a result, we initiated investigations into the compatibility of these systems, first employing the cyclopropenimine-catalysed method. This method was chosen as the [2,3]-Wittig rearrangement was initially optimised to proceed in $CHCl_3$, a solvent proven to be suitable for hydrolysis, and containing only one additional parameter, the catalyst itself, which might influence enzyme performance.

To assess the impact of the Lambert's catalyst **IX** on the enzymatic performance of PLE, experiments using the isolated racemic Wittig product ***rac*-46a** were conducted in two distinct solvent systems: one without the catalyst and another with the addition required for the [2,3]-Wittig rearrangement of 20 mol% of the corresponding catalyst. In the Tris buffer with chloroform as an additive, the reaction proceeded smoothly, exerting no discernible influence on the reaction rate or selectivities. However, the results revealed a significant decrease in conversion when employing the phosphate buffer/DMSO solvent system. This phenomenon may be explained by the aggregation of the catalyst with the enzyme as a visual observation evidenced by the immediate formation of solid particles mixing with these components (Scheme 31).



Scheme 31 *The influence of catalyst* ***IX*** *on hydrolysis; the diastereoselectivity represents a ratio of X:1*

Based on the potential compatibility between catalyst **IX** with enzymatic hydrolysis in the Tris buffer/chloroform solvent system observed in the preceding experiment, an integration of cyclopropenimine-catalysed [2,3]- Wittig rearrangement reaction and PLE-mediated hydrolysis in a one-pot reaction was conducted. To enable a comparison of outcomes, the hydrolysis was simultaneously performed with an isolated Wittig product having an enantiomeric purity (*ee* 49%) equal to that of the *in situ* formed rearranged product. Unfortunately, despite the encouraging earlier findings, the one-pot reaction exhibited a suppression of the biotransformation, demonstrating a substantial decrease in both the diastereoselectivity and enantioselectivity of the minor diastereoisomer. Phosphate buffer was also tested, yielding similar outcomes. Additionally, the same phenomenon of catalyst aggregation was observed in a reaction conducted within the phosphate buffer containing DMSO as a co-solvent (Scheme 32).

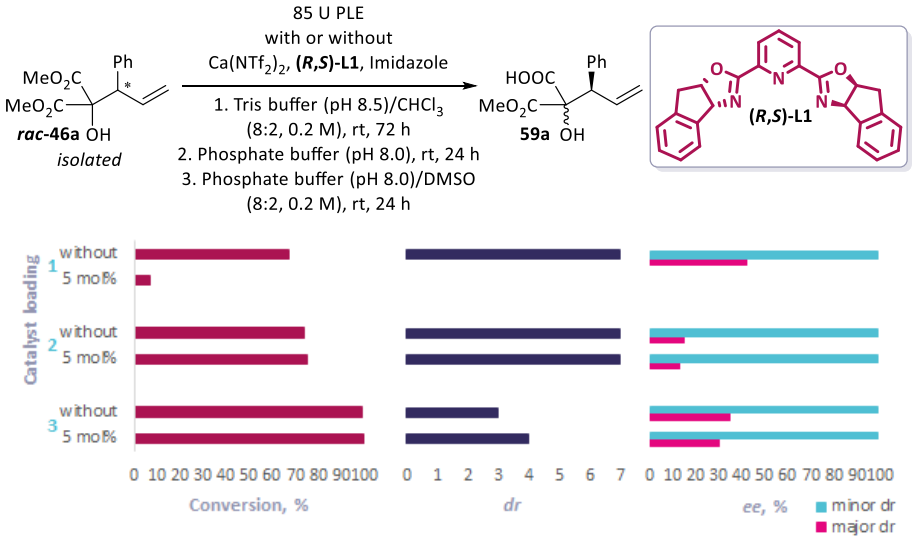


Scheme 32 *Integration of cyclopropenimine-catalysed [2,3]- Wittig rearrangement reaction and PLE-mediated hydrolysis in a one-pot process; the diastereoselectivity represents a ratio of X:1*

3.2.3 Implementation of Ca^{2+}-catalysed [2,3]-Wittig rearrangement/PLE-mediated desymmetrisation in a one-pot reaction

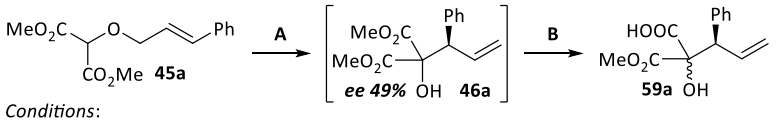
As the combination of the organocatalytic approach with PLE-mediated hydrolysis did not provide the desired results, we explored a possible implementation of Ca^{2+}-catalysed [2,3]-Wittig rearrangement with enzymatic desymmetrisation.

To start with, compatibility experiments were conducted between the Ca^{2+}-catalytic system and PLE. Employing a similar approach as with Lambert catalyst **IX**, hydrolysis experiments were carried out in the presence of a catalytic amount of $Ca(NTf_2)_2$, (*R*,*S*)-inda-PyBox **(*R*,*S*)-L1** and imidazole (5 mol% of each component), using isolated ***rac*-46a** as a starting material. Surprisingly, different trends emerged compared to the outcomes observed with organocatalyst **IX**. A complete inhibition of PLE activity was noted in the Tris buffer/$CHCl_3$ solvent system. In contrast, no discernible influence on hydrolysis results was observed when utilising either a phosphate buffer or a phosphate buffer/DMSO mixture (Scheme 33).



Scheme 33 *The influence of the Ca^{2+}-catalytic system on hydrolysis; the diastereoselectivity represents a ratio of X:1*

The combination of a Ca^{2+}-catalysed [2,3]-Wittig rearrangement with PLE-mediated hydrolysis in a one-pot reaction was performed next. A solvent exchange between two steps was required in this sequential process as the first reaction had to be performed in methanol. This choice of solvent was confirmed as optimal, as it was the only condition in which no transesterification products emerged during the [2,3]-Wittig rearrangement that otherwise interfered with enzymatic hydrolysis, leading to the formation of an inseparable mixture of products. Upon simple evaporation of the methanol, PLE and a corresponding solvent system were added to the reaction mixture initiating the desymmetrisation of the intermediate **46a**. Different buffer systems were evaluated at various temperatures. Gratifyingly, the Ca^{2+}-catalytic system proved suitable for PLE-mediated hydrolysis, revealing phosphate buffer (pH 8.0) containing 20% DMSO at 35 °C to be the optimal conditions for the second step of the one-pot reaction (Scheme 34).

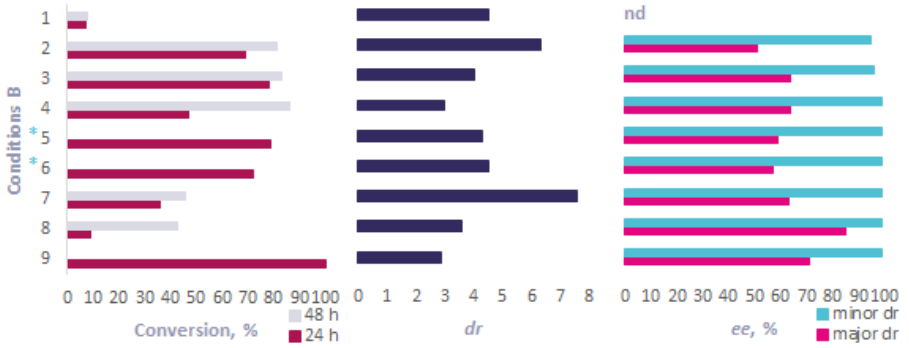


Conditions:

A 5 mol% $Ca(NTf_2)_2$ 0.1 M MeOH
5 mol% **(*R*,*S*)-L1** rt, time
5 mol% Imidazole

B 85 U PLE

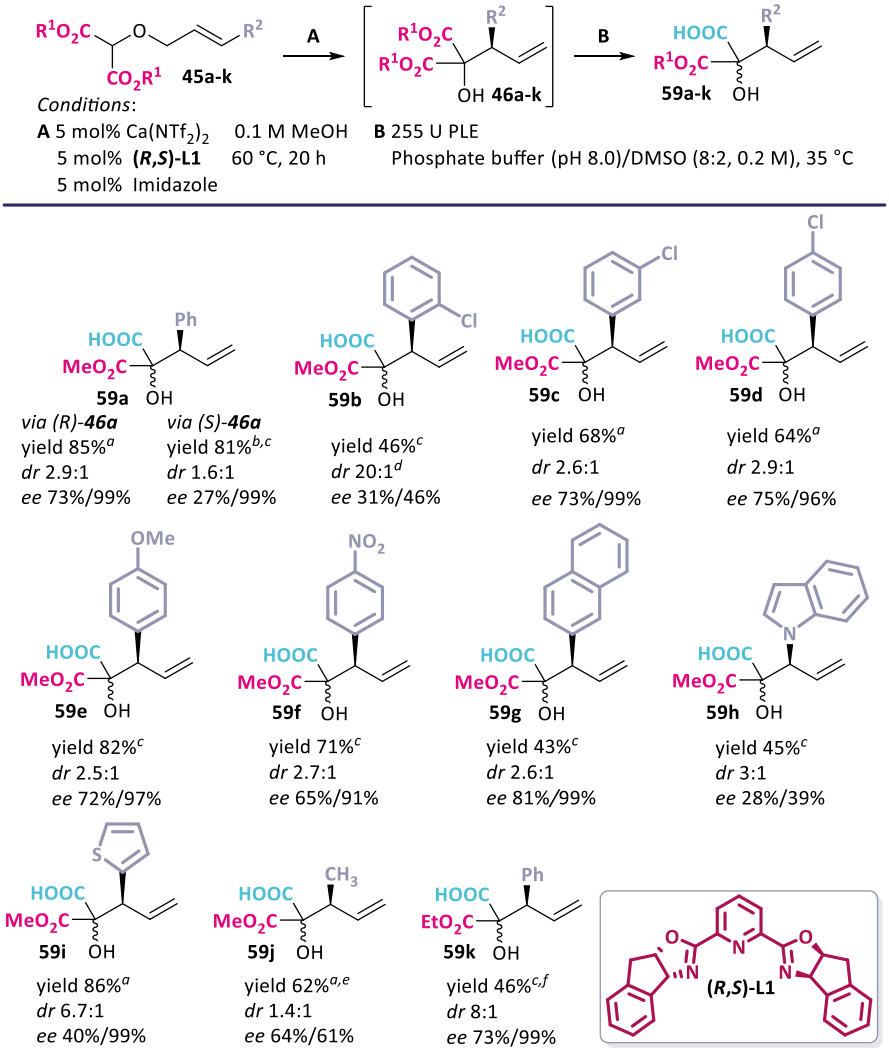
1. Carbonate buffer (pH 8.5)/$CHCl_3$ (8:2, 0.2 M)
2. Tris buffer (pH 8.5) (8:2, 0.2 M)
3. Tris buffer (pH 8.5)/DMSO (8:2, 0.2 M)
4. Carbonate buffer (pH 8.5, 0.2 M)
5. Carbonate buffer (pH 8.5)/DMSO (8:2, 0.2 M)
6. Carbonate buffer (pH 8.5)/DMSO (8:2, 0.2 M), 5 °C
7. Phosphate buffer (pH 8.0, 0.2 M)
8. Phosphate buffer (pH 8.0)/DMSO (8:2, 0.2 M)
9. Phosphate buffer (pH 8.0)/DMSO (8:2, 0.2 M), 35 °C



Scheme 34 *Integration of a Ca^{2+}-catalysed [2,3]- Wittig rearrangement reaction and PLE-mediated hydrolysis in a one-pot process; the diastereoselectivity represents a ratio of X:1, *Conversion remained the same after 24 h*

Subsequently, the scope of the one-pot reaction was investigated. Earlier, while exploring the hydrolysis mediated by PLE with an enantioenriched rearranged product, it was established that achieving a high degree of enantioselectivity required the (*R*)-enantioenriched enantiomer (Table 1). The same pattern emerged in the case of the one-pot process. Specifically, employing the (*S*,*R*)-inda-PyBox **(*S*,*R*)-L1**, which yielded the (*S*)-enantioenriched enantiomer of the intermediate, resulted in a decelerated reaction accompanied by a significant decrease in the enantioselectivity of the half-ester **59a** (*ee* of the major diastereomer 27%). Thus, (*R*,*S*)-ligand **(*R*,*S*)-L1** was utilised in all further experiments. Substitutions on the *meta*- or *para*-positions of the phenyl ring were well tolerated without substantial influence on the overall outcomes (products **59c** – **59f**). Conversely, introducing *ortho*-substitution (**45b**) led to a pronounced enhancement in diastereoselectivity (*dr* 20:1), concomitant with a substantial decrease in the *ee*'s of both diastereomers. Surprisingly, a similar decline in enantioselectivity, coupled with reaction deceleration, was observed when the phenyl ring was replaced with an indanyl moiety (**45h**). At the same time, a substrate with a similarly bulky naphthyl substituent (**45g**) yielded high enantioselectivities for both diastereomers. A plausible explanation for these observations may be connected to differences in the spatial arrangements of substituents, which impact their fitting within the active site of PLE. Utilising a heteroaromatic thienyl group (**45i**) led to enhanced diastereoselectivity, albeit with a lower enantioselectivity for the major diastereomer. Notably, the crotyl-derived **45j** required a prolonged duration of seven days to achieve complete conversion in the [2,3]-Wittig rearrangement, yielding the poor diastereoselectivity of the one-pot

reaction with diminished enantioselectivity of half-ester **59j**. On the other hand, the reaction involving starting material with the bulkier diethyl malonic derivative **45k** was slightly slower, yet yielded the one-pot product **59k** with high enantioselectivities and even greater diastereoselectivity than the analogous dimethyl malonic derivative (Scheme 35).



Reaction conditions: **45a-k** (0.3 mmol), $Ca(NTf_2)_2$ (5 mol%), **(*R,S*)-L1** (5 mol%), imidazole (5 mol%), MeOH (0.1 M) were stirred at 60 °C for 20 h (if not stated otherwise), followed by solvent evaporation and the addition of 255 U of crude PLE, phosphate buffer (pH 8.0)/DMSO (8:2, 0.2 M).; isolated yields after column chromatography. The major diastereomer is depicted in the scheme. The *dr* was determined by the ^{1}H NMR of the crude product. The *ee* was determined by the chiral HPLC of the isolated product. [a] The hydrolysis was completed after 24 h. [b] **(*S,R*)-L1** was used. [c] The hydrolysis was completed after 48 h. [d] Diastereoisomeric ratio of the isolated product is presented. [e] The [2,3]-Wittig rearrangement reaction was completed after seven days. [f] The [2,3]-Wittig rearrangement reaction was conducted in absolute EtOH.

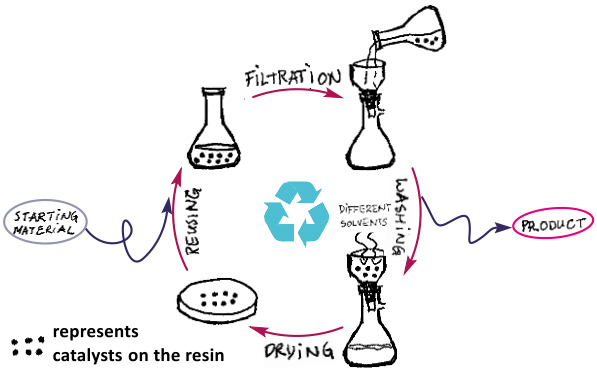
Scheme 35 *The scope of the one-pot reaction*

Overall, the demonstrated method can be considered remarkably robust, as it effectively tolerated a diverse range of substrates with different allylic substituents, especially considering that enzymes typically exhibit an extremely high substrate specificity due to their well-organised and relatively inflexible active sites. Unfortunately, the diastereomers remained indistinguishable in their half-ester form. However, subsequent amidation of the carboxylic acid moiety led to the formation of chromatographically separable diastereomers, making it possible to obtain corresponding amides with high enantioselectivities.

3.3 Primary amines as heterogeneous catalysts in an enantioselective [2,3]-Wittig rearrangement reaction (Publication III and unpublished results)

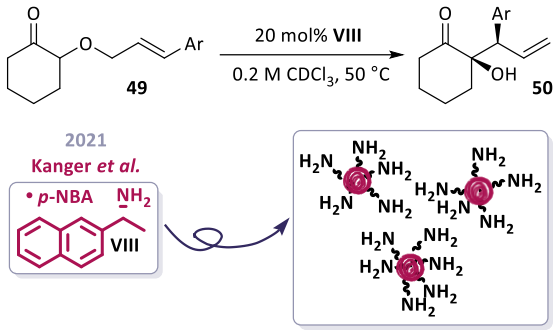
Enhancing performance and reusability have consistently been key factors in the pursuit of the efficient utilisation of natural resources. The United Nations has compiled a list of Sustainable Development Goals that address the problems that need to be overcome and emphasise the importance of continuous improvement. Among the spectrum of objectives, this list includes such concerns as sustainable industrialisation, reasonable consumption, waste production and reusability of materials.[72] The scientific community has the capacity to effect significant changes by improving chemical processes, making them environmentally more sustainable. The field of organocatalysis has proved itself to be very useful in asymmetric synthesis.[73,74] However, one of the biggest obstacles for industry that limits its widespread application is associated with catalyst regeneration.[75] One plausible way to overcome this limitation is by applying heterogeneous catalysis.[76]

The general synthetic methodology involving the utilisation of catalysts immobilised on insoluble resin represents a process characterised by operational simplicity. In this concept, following the completion of the reaction, the reaction mixture should just be filtrated. The desired product is simply recoverable from the supernatant, while the utilised catalyst can be purified through a straightforward washing process involving various solvents, thereby restoring its catalytic efficiency. Upon completion of the drying step, the regenerated catalyst can be re-employed in subsequent reactions involving a fresh batch of the initial starting material (Scheme 36). Fine-tuning of the immobilisation techniques offers the potential for generating a diverse range of chiral organocatalysts on solid support, thus facilitating their recyclability.



Scheme 36 *General concept for synthesis utilising immobilised catalysts*

Our study involved integrating the elucidated approach with the [2,3]-Wittig rearrangement of cyclohexanone derivatives, a reaction previously investigated within our research group.[61] This reaction was selected as a model system due to the possibility of employing structurally simple chiral primary amines as catalysts. Nevertheless, as mentioned above, the optimisation of this rearrangement reaction revealed certain challenges. In particular, it brought to light the significant problem of epimerisation occurring within the product under the rearrangement conditions. This phenomenon had a detrimental impact on the enantioselectivity of the reaction, with a more noticeable effect on the minor diastereomer. Furthermore, typical of organocatalysis, though still noteworthy, a high amount of catalyst (20 mol%) was required to achieve the desired reaction efficacy. Thus, to overcome those limitations, we envisioned a promising strategy involving using amino acids anchored to resin support as catalysts (Scheme 37).



Scheme 37 *General concept of the use of immobilised catalysts for the [2,3]-Wittig rearrangement of cyclohexanone derivatives* ***49***

3.3.1 Synthesis of the immobilised catalysts

Numerous techniques exist for anchoring organic molecules on insoluble resin matrices. The available strategies allow for the introduction of various chemical bonds between the organic moieties and the resin, offering the flexibility to incorporate structurally diversified linkers of variable lengths. For this study, a range of catalysts attached to diverse resins was prepared with the aim of determining the influence of these parameters on the catalytic efficacy of the immobilised catalysts in the corresponding rearrangement reaction. Cross-linked polystyrene-based resins were employed in all cases to ensure the heterogeneous nature of the catalysts. All synthesised catalysts were characterised by IR analysis, and their loadings were quantified via elemental analysis (Scheme 38).

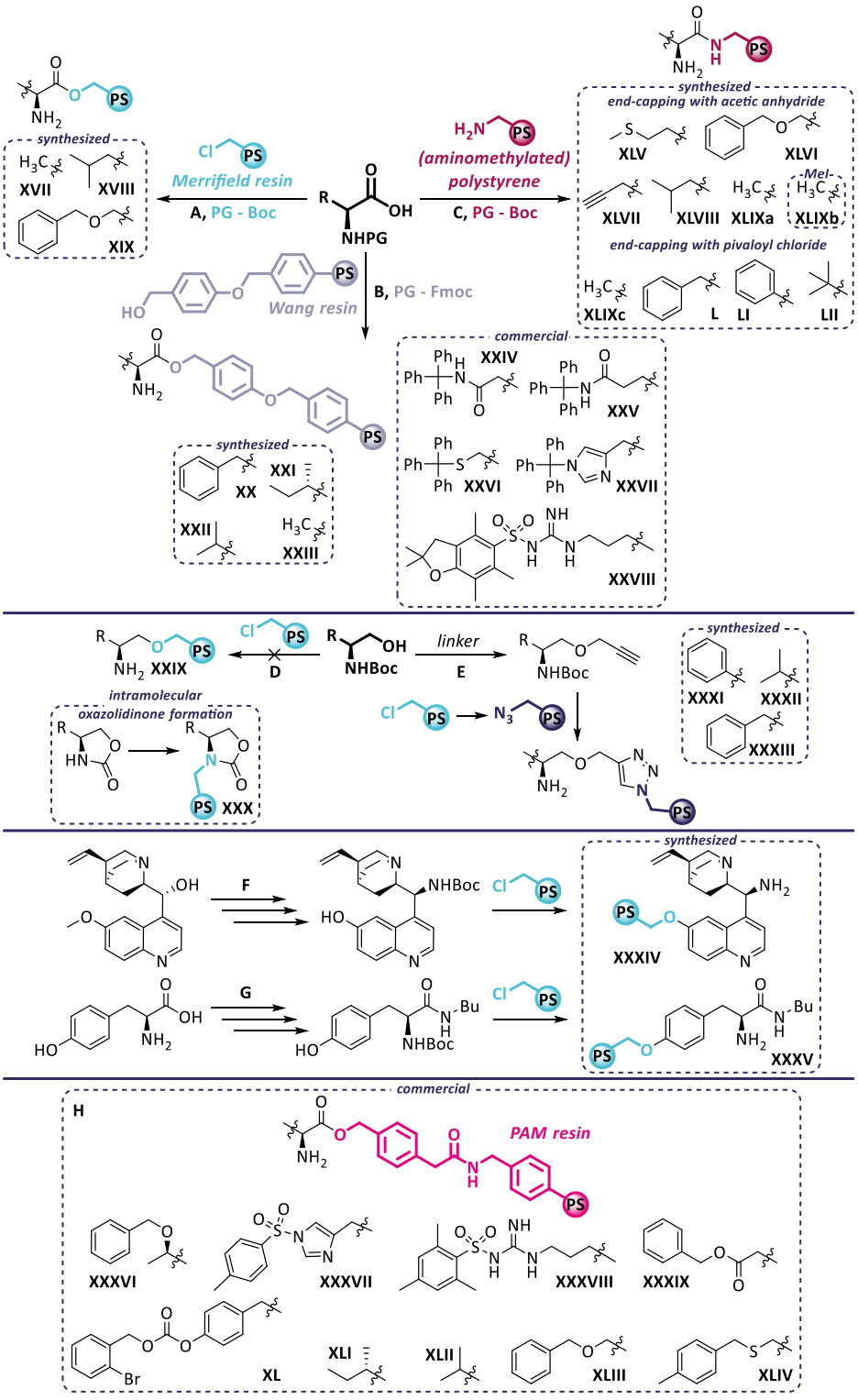
Three distinct methodologies were used to immobilise amino acids on the resins. Firstly, the Boc-protected amino acids were covalently anchored to the widely known Merrifield resin. This conjugation involved nucleophilic displacement of the chlorine atom facilitated by potassium fluoride, which activated the corresponding carboxylic acid moieties of amino acids, yielding catalysts **XVII** – **XIX** with loadings in the range of 0.59 – 0.64 mmol/g (Scheme 38, A). Subsequently, a Wang resin bearing a hydroxy group was functionalised with Fmoc-protected amino acids. This entailed the utilisation of the classic peptide coupling system hydroxybenzotriazole (HOBt)/*N*,*N*'-diisopropylcarbodiimide (DIC). To eliminate possible interference from residual free hydroxy groups on the resin, an additional blocking step employing acetic anhydride was conducted, affording

catalysts **XX** – **XXIII**, exhibiting loadings ranging from 0.38 to 0.69 mmol/g (Scheme 38, B). Utilising the same coupling system, the introduction of Boc-protected amino acids to (aminomethylated)polystyrene was carried out. This variation sought to discern the influence of the attachment bond between the catalytic moiety and the resin. Herein, three different strategies were employed to block the remaining free amino groups of the resin, which otherwise could have participated in the reaction, leading to a racemic background reaction. These protocols yielded a series of immobilised catalysts **XLV** to **LII**, end-capped with acetic and pivaloyl moieties or alkylated with methyl iodide. The obtained catalysts exhibited comparable functionalisation levels, falling within the range of 0.38 – 0.59 mmol/g (Scheme 38, C).

In pursuit of a comprehensive exploration of the effects of anchoring bonds, a set of amino acids was transformed into the corresponding amino alcohols. These amino alcohols were then used for direct attachment to the Merrifield resin via nucleophilic substitution mediated by sodium hydride. Regrettably, this approach proved unsuccessful, as the intramolecular addition of the deprotected alcohol to the Boc-protecting group caused the formation of an oxazolidinone ring attached to the resin (compound **XXX**, Scheme 38, D). Despite this obstacle, the ether bond was introduced by adding a linker with a terminal triple bond. This linkage was incorporated into the azide analogue of the Merrifield resin via click chemistry, resulting in catalysts **XXXI** to **XXXIII**, bearing triazole rings with slightly higher loadings, ranging from 0.63 to 0.72 mmol/g (Scheme 38, E).

Two independent catalysts **XXXIV** and **XXXV** integrated into the Merrifield resin were also synthesised. To ascertain the potential influence of the bulkiness of the primary amine on the enantioselectivity of the rearrangement reaction, catalyst **XXXIV**, derived from quinine, was prepared. This involved a multi-step procedure, resulting in a functionalisation level of 0.6 mmol/g (Scheme 38, F). In addition, the presence of a free hydroxy group made it possible to anchor modified tyrosine as well, yielding catalyst **XXXV**, albeit with a relatively low loading of 0.34 mmol/g (Scheme 38, G).

Within this study, a range of commercially available catalysts were also incorporated. These catalysts were immobilised on Wang (Scheme 38, B, commercial) or PAM resins (Scheme 38, H, commercial), distinguished by variations in the linker functionality connecting the organic moiety and the polystyrene resin. A deprotection step for the amino group was necessary to obtain the active catalysts, as primary amines are essential for the [2,3]-Wittig rearrangement reaction.



Scheme 38 *Synthesised and commercial catalysts on the resins used in this work*

3.3.2 Application of the immobilised catalysts in the [2,3]-Wittig rearrangement of cyclohexanone derivatives

Subsequently, the comprehensive set of synthesised and commercially available catalysts was implemented in the asymmetric catalytic [2,3]-Wittig rearrangement of cyclohexanone derivatives **49**. The previously established conditions, which had been optimised for homogeneous catalysis, were employed as the initial reference for this study. Specifically, 20 mol% of the corresponding heterogeneous catalyst and *para*-nitrobenzoic acid were shaken in 0.2 M $CDCl_3$ at 300 rpm and 50 °C, yielding the product **(*S*,*S*)-50a** (Scheme 39).

Attempting to derive meaningful information regarding the impact of catalyst substituents on the outcome of the rearrangement reaction proved complex. Overall, catalysts **XVII** to **XIX**, linked through an ester bond to the Merrifield resin, exhibited moderate activity levels (conversions 48 – 80%). Regrettably, these catalysts yielded products with notably low enantioselectivities for both diastereomers. Likewise, catalysts **XX** – **XXVIII**, integrated into the Wang resin characterised by an ether-bonded linker, demonstrated similar limitations in enantioselectivity. However, interestingly, an acceleration of the reaction rate was observed when catalysts with bulkier substituents bearing trityl fragments were employed.

Catalysts **XXXVI** – **XLIV** immobilised on the PAM resin yielded reasonable conversions, ranging from 30% to 78%. However, it appeared that the functionality of the resin's linker of these catalysts had a comparatively modest influence on the selectivity of the reaction as the products were obtained with relatively low enantioselectivities.

Surprisingly, despite our expectations for catalysts **XXXI** – **XXXIII**, attached via the triazole moiety, these catalysts showed minimal catalytic activity in the rearrangement reaction, yielding only 5 – 6% conversion. A plausible explanation for this outcome was connected to the degradation of catalysts under the rearrangement conditions, as a noticeable colour change was observed after several hours of heating the reaction.

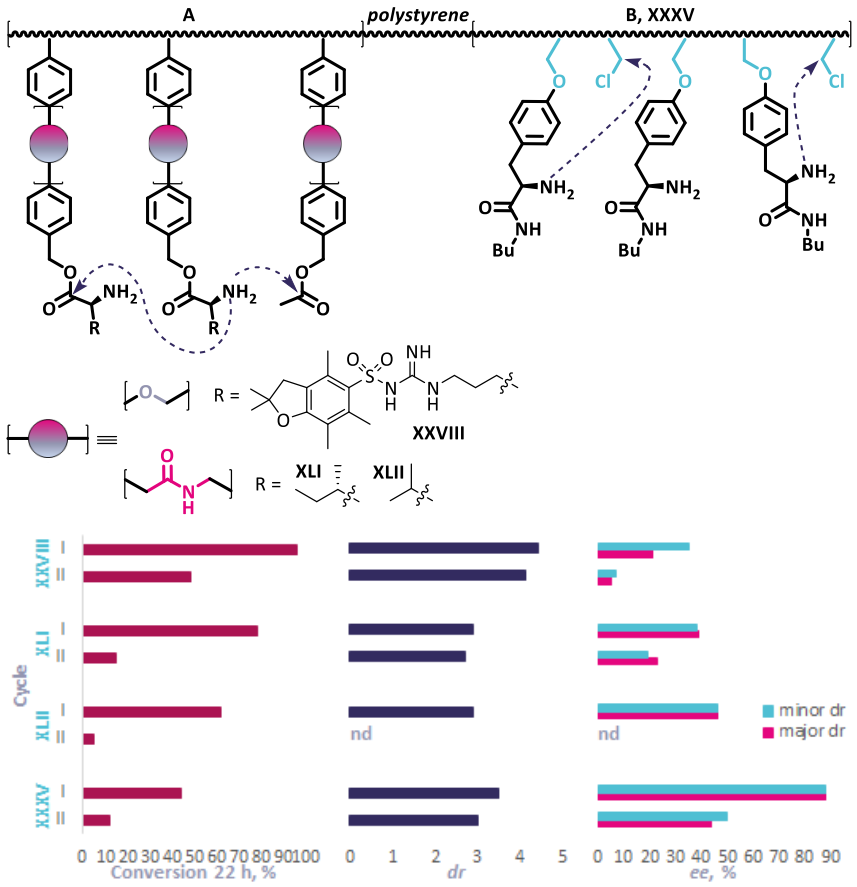
Catalyst **XXXIV**, derived from the bulkier *Cinchona alkaloid*, increased the enantioselectivities of the products, although this enhancement was accompanied by a mere 7% conversion rate. Conversely, catalyst **XXXV**, prepared from tyrosine, not only enhanced enantioselectivities but also exhibited reactivity sufficient for further optimisation. This finding led to the hypothesis that the adjacency of the amide's proton to the catalytic primary amine might produce a cooperative effect, contributing to enhanced stereoinduction. Consequently, the series of catalysts **XLV** – **LII** linked through an amide bond was synthesised and subsequently applied. Gratifyingly, redesigning catalysts enhanced the enantioselectivities for the desired products, in addition to good to excellent conversions rates to the [2,3]-Wittig rearrangement product.

Scheme 39 *Screening of immobilised catalysts in the [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives 49a; the diastereoselectivity represents a ratio of X:1*

3.3.3 Recyclability of the immobilised catalysts

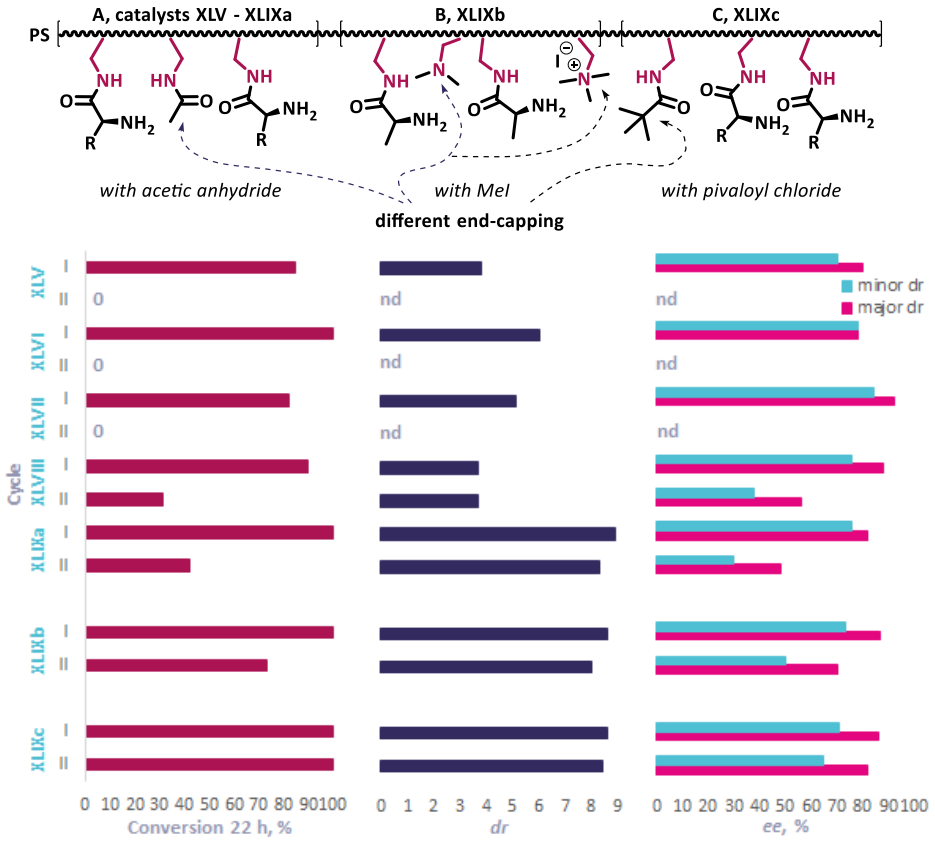
Given that the principal objective of immobilising the catalysts on the resin involved enabling their repeated use, a comprehensive study on recyclability was conducted. All catalysts used in the recycling study underwent filtration upon the completion of the [2,3]-Wittig rearrangement reaction. Following filtration, they were subjected to a washing procedure employing $CHCl_3$ and MeOH, followed by 24 hours of vacuum drying. Subsequently, a new cycle of the rearrangement reaction was initiated by introducing a fresh batch of reactants.

Initially, our investigation aimed to assess the possibility of recycling catalysts anchored to the resin through ester bonds. Among this series, the catalysts **XXVIII**, **XLI** and **XLII**, which exhibited the most promising performance, were isolated after the first reaction cycle, and were subjected to a subsequent rearrangement reaction. In all cases, reduced reactivity and diminished enantioselectivities of both diastereomers were observed after the second cycle. To explain these outcomes, we conducted elemental analysis, IR spectroscopy and SEM on the reused catalysts. Notably, no evidence of a leakage of the organic component from the immobilised catalysts was detected, as indicated by consistency in the nitrogen content between freshly prepared catalysts and those subjected to the second cycle. Nevertheless, the IR spectra revealed an additional band in the carbonyl region (see Publication III, Figure 1). This observation led us to infer the occurrence of intramolecular amidation reactions involving the primary amine, either with another amino acid moiety or an acetyl group formed during the end-capping process. Consequently, this could result in the blockage of the catalytic sites (Scheme 40, A). Given these findings, we also explored the reusability of catalyst **XXXV**, which was linked to the resin through an ether bond. Despite the absence of ester moieties in this catalyst, a similar pattern emerged, with a deceleration of the reaction and a decrease in the enantiomeric excess of the product. In this case, SEM analysis revealed the presence of unreacted chloride moieties, which could have contributed to the alkylation of the primary amines. Unfortunately, efforts to enhance the reusability of catalyst **XXXV** were unsuccessful, as we could not eliminate the unreacted chloride, even after the application of end-capping (Scheme 40, B).



Scheme 40 *Recyclability study with ester- and Merrifield-bonded catalysts and a plausible deactivation mechanism; the diastereoselectivity represents a ratio of X:1*

Thus, we proceeded with further investigations into recyclability, employing the amide-bonded catalysts **XLV** to **XLIXa**, which were end-capped with acetic moieties. Despite these catalysts being designed to be devoid of ester moieties and, therefore, the possibility of alkylation, reusability was not achieved. Consistent with our previous observations with ester-bonded catalysts, the emergence of an additional carbonyl band in the IR spectra was detected. This observation indicated the potential occurrence of an undesired intramolecular acyl-shift connected to the end-capping process (Scheme 41, A). Furthermore, catalyst **XLIXb**, which underwent end-capping via alkylation with methyl iodide, showed slightly more promising results. A decline in conversion and enantioselectivities remained evident after the second cycle, indicating that it could not be effectively reused again (Scheme 41, B). Next, an end-capping strategy utilising bulkier pivaloyl chloride was applied, yielding catalyst **XLIXc**. Encouragingly, catalyst **XLIXc** exhibited reactivity and selectivity similar to the previously examined catalysts **XLIXa** and **XLIXb** during the first cycle while maintaining their productivity in the second cycle. (Scheme 41, C).



Scheme 41 *Recyclability study with amide-bonded catalysts and different end-capping strategies; the diastereoselectivity represents a ratio of X:1*

After identifying a suitable end-capping method that did not hinder catalytic activity, thereby enabling the successful completion of the second cycle of the [2,3]-Wittig rearrangement reaction, we turned to assessing the potential number of cycles achievable with the same catalyst. To this end, from the series of amide-bonded catalysts that were end-capped with pivaloyl chloride, we selected the most promising catalysts, **XLIXc** and **L**. Interestingly, despite the stability of catalyst **XLIXc** during four cycles of the rearrangement reaction, we observed a rapid decline in activity during the fifth cycle, indicated by a decrease in conversion and selectivities (Figure 1, A). Conversely, catalyst **L** exhibited better stability, managing six cycles of the rearrangement reaction without significant variations in the reaction outcomes. However, starting with the seventh cycle, a noticeable decrease in the conversion became apparent, although, in comparison to catalyst **XLIXc**, without a decrease in diastereo- or enantioselectivities (Figure 1, B). In addition, a simplified isolation procedure was developed, involving just filtration and basic extraction of the resultant supernatant, which yielded the pure product **(*S*,*S*)-50a** with an 84% yield. It is worth noting that the epimerisation problems, observed during the reaction with homogeneous catalyst were also eliminated, as the enantioselectivities of the obtained product **(*S*,*S*)-50a** remained the same (see: Publication III, Figure 6).

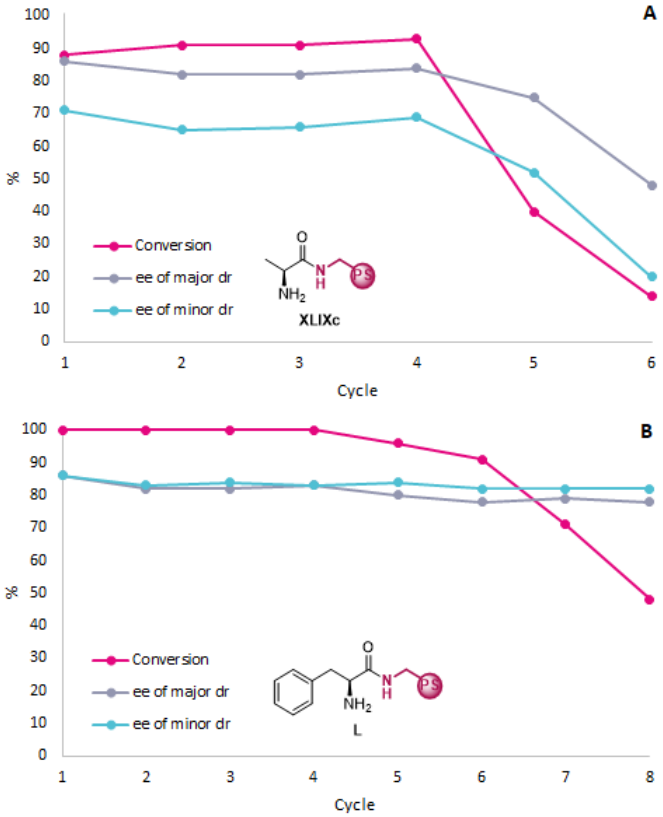


Figure 1 *Recycling study with catalysts* ***XLIXc*** *(A) and* ***L*** *(B)*

Despite successfully designing reusable immobilised catalysts, their activity eventually declined. To determine the underlying reasons for this decline, we conducted elemental analysis, SEM and IR spectroscopy on both freshly prepared and reused catalysts **XLIXc** and **L**. Both catalysts' elemental analysis and SEM did not reveal any significant differences, whereas notable changes were detected in the IR spectra. As observed previously, an additional carbonyl band appeared (1706 cm^{-1}). However, only in the case of catalysts attached to the (aminomethylated)polystyrene did a distinctive band emerge, at 2245 cm^{-1}, characteristic to carbamate functional groups. This observation suggested that the primary amines within catalysts **XLIXc** and **L** reacted with CO_2 under the [2,3]-Wittig rearrangement conditions, leading to the formation of corresponding carbamate derivatives as deactivated catalysts (Figure 2).[77,78]

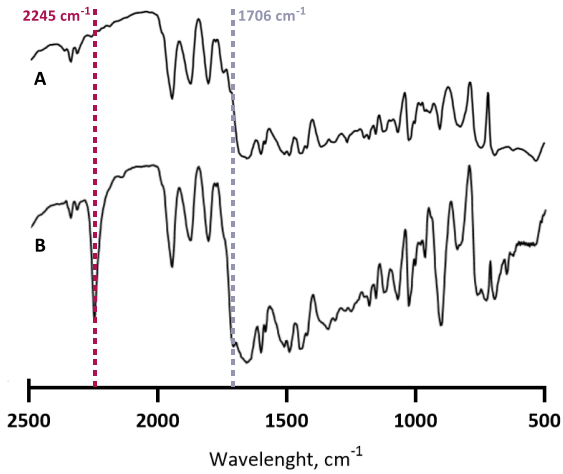


Figure 2 *Outtakes from the IR spectra of initial (A) and six times-recycled (B) catalyst* ***L***

In summary, highly performing and reusable catalysts immobilised on the (aminomethylated)polystyrene were designed. Therefore, utilising their recyclability, we improved the efficiency of the asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives **49**.

4 Conclusions

- A rapid and highly diastereoselective auxiliary-based [2,3]-sigmatropic rearrangement reaction of ammonium ylides was developed leading to the formation of non-natural amino acid analogues (*dr* up to 15.7:1).
- Two different catalytic systems were tested for compatibility with enzymatic catalysis. The combination of an organocatalytic cyclopropenimine-based [2,3]-Wittig rearrangement reaction of malonate derivatives with enzymatic desymmetrisation showed strong inhibition of the PLE. However, PLE remained active in the presence of a Ca^{2+}-catalytic system.
- A chemoenzymatic one-pot method for the implementation of an asymmetric Ca^{2+}-catalysed [2,3]-Wittig rearrangement reaction of malonate derivatives with enzymatic desymmetrisation was developed. This method allowed for the synthesis of structurally complex and diverse α-branched half-esters containing vicinal quaternary-tertiary stereocentres with high diastereoselectivities (up to 20:1), good enantioselectivities of the major diastereomers (up to 81%) and excellent enantioselectivities of the minor diastereomers (up to 99%).
- Various polystyrene-supported heterogeneous chiral aminocatalysts were prepared for the [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives and were characterised by elemental analysis, IR and SEM. Among these immobilised catalysts, (aminomethylated)polystyrene-based aminocatalysts exhibited the best catalytic performance in terms of activity and enantioselectivity, resulting in full conversion of the rearranged products with enantiomeric purity of up to 86% for both diastereomers.
- Two parameters influenced the recyclability of the designed catalysts:
    - The attachment bond. Catalysts prepared through the implementation via an ester bond were prone to an intramolecular trans-amidation reaction, which led to the deactivation of the catalytic primary amines.
    - Bulkiness of the end-capping moiety. Catalysts end-capped with an acetyl group led to diminished reactivity and selectivities in the second cycle. However, using pivaloyl chloride to block unprotected amino groups of (aminomethylated)polystyrene resin allowed to improve the reusability of the catalysts. Catalyst **L** showed excellent catalytic performance in six consecutive cycles without any sign of deactivation.
- The recovery of the (aminomethylated)polystyrene-based catalysts from the reaction mixture was achieved through a filtration and washing sequence. Therefore, a straightforward procedure involving basic extraction was sufficient to separate the pure cyclic α-hydroxyketone rearranged product **(*S*,*S*)-50a** in 84% yield.

5 Experimental

Example of the general procedure with model compound *trans*-55b for the diastereoselective [2,3]-sigmatropic rearrangement reaction of ammonium salts (Publication I)

The suspension of ammonium salt ***trans*-55b** (74 mg, 0.2 mmol) and TBD (30.6 mg, 0.22 mmol) in $CHCl_3$ (0.8 mL) was stirred at rt for 1 min. The crude mixture was concentrated and purified by column chromatography (5 – 15% EtOAc/DCM) affording product **56b** (55 mg, 95%) as a white solid.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 4 H, Ar), 7.21–7.15 (m, 1 H, Ar), 5.84 (ddd, *J* = 17.1, 10.1, 8.9 Hz, 1 H, CH_2CH), 5.36 (d, *J* = 11.3 Hz, 1 H, COCH), 5.02 (dt, *J* = 17.0, 1.0 Hz, 1 H, CH_2CH), 4.92 (dd, *J* = 10.1, 1.4 Hz, 1 H, CH_2CH), 4.38–4.29 (m, 2 H, CH_2O), 4.06–3.88 (m, 2 H, CH_2N), 3.79 (dd, *J* = 11.2, 8.9 Hz, 1 H, ArCH), 2.22 (s, 6 H, $N(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 153.6, 140.9, 138.7, 128.6 (2 C), 128.1 (2 C), 126.7, 116.8, 65.2, 61.9, 50.4, 42.1, 41.2 (2 C).

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 4 H), 7.21–7.15 (m, 1 H), 6.12 (ddd, *J* = 16.5, 10.7, 8.6 Hz, 1 H), 5.29 (d, *J* = 11.5 Hz, 1 H), 5.12–5.09 (m, 1 H), 5.09–5.05 (m, 1 H), 4.20–4.09 (m, 1 H), 3.95–3.87 (m, 1 H), 3.77–3.71 (m, 2 H), 3.52–3.35 (m, 1 H), 2.41 (s, 6 H).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NaN_2O_3$: 311.1366; found: 311.1371.

Example of the general procedure with model compound 45a for the chemoenzymatic one-pot synthesis of α-hydroxy half-esters (Publication II)

To a solution of dimethyl 2-(cinnamyloxy)malonate **45a** (79 mg, 0.3 mmol) in methanol (3 mL), $Ca(NTf_2)_2$ (9 mg, 0.015 mmol), (*R,S*)-inda-PyBox (5.9 mg, 0.015 mmol), and imidazole (1 mg, 0.015 mmol) were added. The reaction mixture was stirred at 60 °C for 20 h. After evaporation of the solvent, the crude intermediate ***trans*-46a** was suspended in DMSO (0.3 mL) and sodium phosphate buffer (pH 8.0, 1.2 mL). PLE (255 U) was added, and the mixture was stirred at 35 °C for 24 h. It was then acidified to pH 2 with 1 M aq HCl solution and extracted with diethyl ether. The combined organic layers were dried over MgSO4. After filtration, the solvent was removed in vacuo, and the crude carboxylic acid was purified by column chromatography on silica gel (2% EtOAc in DCM, followed by 2% EtOAc in the DCM/formic acid 99/1 mixture), providing product **59a** (64 mg, 85%) as an off-white solid.

Major diastereoisomer: *ee* 73% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 39.0 min and t_R (minor) = 34.9 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H, ArH), 6.15 (ddd, *J* = 17.1, 10.2, 9.0 Hz, 1H, $CHCH_2$), 5.30−5.19 (m, 2H, CH_2), 4.32 (d, *J* = 9.0 Hz, 1H, CHAr), 3.69 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 137.3, 134.0, 129.0 (2C), 128.7 (2C), 128.0, 119.8, 83.1, 55.3, 54.3.

Minor diastereoisomer: *ee* 99% [Chiralpak AD-H, hexane (TFA 0.01%)/IPrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 68.7 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.20 (m, 5H, ArH), 6.21−6.07 (m, 1H, $CHCH_2$), 5.22−5.17 (m, 2H, CH_2), 4.31 (d, *J* = 9.3 Hz, 1H, CHAr), 3.92 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 137.0, 134.7, 129.4 (2C), 128.6 (2C), 127.9, 119.1, 82.9, 55.2, 54.7.

HRMS (ESI): m/z $[M- H]^-$ calcd for $C_{13}H_{13}O_5$: 249.0768; found: 249.0772.

Example of the general procedure of the use of heterogeneous catalysts with model compound 49a for the enantioselective [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives (Publication III)

To a solution of 2-(cinnamyloxy)cyclohexan-1-one **49a** (0.24 mmol, 55 mg) in $CDCl_3$ (1.2 mL), catalyst **XXIX** (f = 0.38 mmol/g, 0.048 mmol, 126 mg) and *p*-NBA (0.048 mmol, 8 mg) were added. The reaction mixture was shaken at 50 °C for 16 h. The polystyrene-supported catalyst was removed by filtration and the sat. aq. $NaHCO_3$ (5 mL) was added to the supernatant. Then, the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the product **(S,S)-50a** (46 mg, 84%) as a white amorphous solid.

Major diastereomer: *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35 °C, l = 210 nm; t_R (major) = 7.7 min and t_R (minor) = 11.8 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 2H, ArH), 7.35–7.27 (m, 2H, ArH), 7.26–7.20 (m, 1H, ArH), 6.60 (dt, *J* = 15.8, 1.5, 1H, CHAr), 6.30 (ddd, *J* = 15.9, 6.5, 5.8, 1H, CH_2CH), 4.37 (ddd, *J* = 12.6, 5.8, 1.5, 1H, OCH_2), 4.13 (ddd, *J* = 12.6, 6.5, 1.4, 1H, OCH_2), 3.93 (ddd, *J* = 10.3, 5.5, 1.3, 1H, $CHOCH_2$), 2.63–2.45 (m, 1H, CH_2), 2.37–2.17 (m, 2H, CH_2), 2.08–1.90 (m, 2H, CH_2), 1.88–1.60 (m, 3H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.3, 136.7, 133.0, 128.7, 127.9, 126.7, 125.8, 81.8, 70.6, 40.8, 34.7, 27.8, 23.4.

Minor diastereomer: *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35 °C, l = 210 nm; t_R (major) = 34.6 min and t_R (minor) = 9.8 min].

Compound XXX (R = Ph, *sec*Bu)

Merrifield resin (200 mg, *f* = 1.02 mmol/g) with KI (3.4 mg, 0.02 mmol) were suspended in 4 mL DMF and allowed to swell for 20 min. Corresponding aminoalcohol (0.24 mmol) and sodium hydride (12 mg, 0.31 mmol, 60% in mineral oil) were added to the suspension, and the reaction mixture was shaken at 50 °C for 48 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

R = Ph
IR (KBr): v 1748 cm^{-1} (Carbonyl band of oxazolidinone moiety)

R = *sec*Bu
IR (KBr): v 1735 cm^{-1} (Carbonyl band of oxazolidinone moiety)

Catalysts XXXI – XXXIII

Preparation of the azide-analog of the Merrifield resin

Merrifield resin (3 g, *f* = 1.02 mmol/g) was suspended in 30 mL DMF and allowed to swell for 20 min. Sodium azide (4.55 g, 70 mmol) was added to the suspension, and the reaction mixture was shaken at 60 °C for 24 h. The solid was filtered and washed successively with H_2O, THF, MeOH:THF (1:1), MeOH, and THF. The solid was dried in vacuo for 24 h.

IR (KBr): v 2088 cm^{-1} (azide band)

N elemental analysis: 4 %, *f* = 0.95 mmol/g.

Click-reaction

Azide-analogue of the Merrifield resin (200 mg, *f* = 1.02 mmol/g) was suspended in 5 mL DMF:THF (1:1) and allowed to swell for 20 min. Corresponding alkyl amino alcohol (2 eq), DIPEA (79 mg, 0.612 mmol), and CuI (1.9 mg, 0.0102 mmol) were added to the suspension and the reaction mixture was shaken at 35 °C for 24 h. The solid was filtered and washed successively with THF, H_2O, THF, MeOH:THF (1:1), MeOH, and THF. The solid was dried in vacuo for 24 h.

Catalyst **XXXI Ph**

IR (KBr): v 1707 cm^{-1} (Carbonyl band of Boc-protecting group, before deprotection)

N elemental analysis: 4.32 %, *f* = 0.77 mmol/g.

Catalyst **XXXII Val**

IR (KBr): v 1708 cm^{-1} (Carbonyl band of Boc-protecting group, before deprotection)

N elemental analysis: 4.01 %, *f* = 0.72 mmol/g.

Catalyst **XXXIII Bn**

IR (KBr): v 1708 cm^{-1} (Carbonyl band of Boc-protecting group, before deprotection)

N elemental analysis: 3.89 %, *f* = 0.69 mmol/g.

Table 2 *Supporting information concerning compounds discussed in the thesis but not presented in the Experimental section can be found in the corresponding publications.*

Entry	Compound number in thesis	Compound number in publication		
		I	**II**	**III**
1	**(*R*,*S*)-L1**		**(*R*,*S*)-inda-PyBox**	
2	**IX**		**I**	
3	**XVII**			**I**
4	**XVIII**			**II**
5	**XIX**			**III**
6	**XX**			**IV**
7	**XXI**			**V**
8	**XXII**			**VI**
9	**XXIII**			**VII**
10	**XXIV**			**VIII**
11	**XXV**			**IX**
12	**XXVI**			**X**
13	**XXVII**			**XI**
14	**XXVIII**			**XII**

15	**XXXIV**			**XXII**
16	**XXXV**			**XXIII**
17	**XXXVI**			**XIII**
18	**XXXVII**			**XIV**
19	**XXXVIII**			**XV**
20	**XXXIX**			**XVI**
21	**XL**			**XVII**
22	**XLI**			**XVIII**
23	**XLII**			**XIX**
24	**XLIII**			**XX**
25	**XLIV**			**XXI**
26	**XLV**			**XXIV**
27	**XLVI**			**XXV**
28	**XLVII**			**XXVI**
29	**XLVIII**			**XXVII**
30	**XLIXa**			**XXVIIIIa**
31	**XLIXb**			**XXVIIIIb**
32	**XLIXc**			**XXVIIIIc**
33	**L**			**XXIX**
34	**LI**			**XXX**
35	**LII**			**XXXI**
36	**45a**		**1a**	
37	**45b**		**1b**	
38	**45c**		**1c**	
39	**45d**		**1d**	
40	**45e**		**1e**	
41	**45f**		**1f**	
42	**45g**		**1g**	
43	**45h**		**1h**	
44	**45i**		**1i**	
45	**45j**		**1j**	
46	**45k**		**1k**	
47	**(*R*)-46a**		**(*R*)-2a**	
48	**(*S*)-46a**		**(*S*)-2a**	
49	**46b**		**2b**	
50	**46c**		**2c**	
51	**46d**		**2d**	
52	**46e**		**2e**	
53	**46f**		**2f**	
54	**46g**		**2g**	
55	**46h**		**2h**	
56	**46i**		**2i**	
57	**46j**		**2j**	
58	**46k**		**2k**	
59	**49a**			**1**
60	**(*S*,*S*)-50a**			**2**

61	**55a**	**1a**		
62	***trans*-55b**	***trans*-1b**		
63	***cis*-55b**	***cis*-1b**		
64	**55c**	**1c**		
65	**55d**	**1d**		
66	**55e**	**1e**		
67	**55f**	**1f**		
68	***trans*-55g**	***trans*-1g**		
69	***cis*-55g**	***cis*-1g**		
70	**55h**	**1h**		
71	**55i**	**1i**		
72	**55j**	**1j**		
73	**55k**	**1k**		
74	**55l**	**1l**		
75	**55m**	**1m**		
76	**56a**	**2a**		
77	**56b**	**2b**		
78	**56c**	**2c**		
79	**56d**	**2d**		
80	**56e**	**2e**		
81	**56f**	**2f**		
82	**56g**	**2g**		
83	**56h**	**2h**		
84	**56i**	**2i**		
85	**56j**	**2j**		
86	**56k**	**2k**		
87	**56l**	**2l**		
88	**56m**	**2m**		
89	**57**	**3**		
90	**58**	**4**		
91	**59a**		**3a**	
92	**59b**		**3b**	
93	**59c**		**3c**	
94	**59d**		**3d**	
95	**59e**		**3e**	
96	**59f**		**3f**	
97	**59g**		**3g**	
98	**59h**		**3h**	
99	**59i**		**3i**	
100	**59j**		**3j**	
101	**59k**		**3k**	

References

(1) Rojas, C. M. *Molecular Rearrangements in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2015**. doi:10.1002/9781118939901

(2) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci.* **2008**, *105*, 13197–13202. doi:10.1073/pnas.0804348105

(3) Hock, K. J.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 13566–13568. doi:10.1002/anie.201707092

(4) Fleming, I. *Pericyclic Reactions*; Oxford University Press, **1998**

(5) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446–7479. doi:10.1021/acscatal.5b02070

(6) Smith, M. B.; March, J. *Advanced Organic Chemistry*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2006**. doi:10.1002/0470084960

(7) Seashore-Ludlow, B.; Somfai, P. Sigmatropic Rearrangements in Stereoselective Synthesis. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2013**; pp 1–26. doi:10.1002/9781118596784.ssd017

(8) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563–572. doi:10.1002/anie.197905633

(9) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860. doi:10.1021/cr00098a009

(10) Colomer, I.; Velado, M.; Fernández De La Pradilla, R.; Viso, A. *Chem. Rev.* **2017**, *117*, 14201–14243. doi:10.1021/acs.chemrev.7b00428

(11) Nishibayashi, Y.; Uemura, S. Selenoxide Elimination and [2,3]-Sigmatropic Rearrangement. In *Organoselenium Chemistry*; Wirth, T., Ed.; Wiley, **2011**; pp 287–320. doi:10.1002/9783527641949.ch7

(12) Bao, H.; Qi, X.; Tambar, U. *Synlett* **2011**, *2011*, 1789–1792. doi:10.1055/s-0030-1260962

(13) Clark, J. S. *Nitrogen, Oxygen, and Sulfur Ylide Chemistry: A Practical Approach in Chemistry*; Oxford University Press, **2002**

(14) Jana, S.; Guo, Y.; Koenigs, R. M. *Chem. – Eur. J.* **2021**, *27*, 1270–1281. doi:10.1002/chem.202002556

(15) Tayama, E. *Chem. Rec.* **2015**, *15*, 789–800. doi:10.1002/tcr.201500009

(16) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193–3197. doi:10.1039/JR9280003193

(17) Millard, B. J.; Stevens, T. S. *J. Chem. Soc.* **1963**, 3397–3403. doi:10.1039/jr9630003397

(18) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066–1067. doi:10.1021/ja043768i

(19) Hill, R. K. Chirality Transfer via Sigmatropic Rearrangements. In *Asymmetric Synthesis: Stereodifferentiating Addition Reactions, Part B*; Morrison, J. D., Ed.; Elsevier: Academic Press, London, **1984**; Vol. 3, pp 503–572

(20) Tayama, E. *Heterocycles* **2016**, *92*, 793. doi:10.3987/REV-16-837

(21) Vedejs, E.; Arco, M. J.; Renga, J. M. *Tetrahedron Letters* **1978**, *6*, 523–526. doi:10.1016/S0040-4039(01)85322-3

(22) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185–1190. doi:10.1021/jo00400a035

(23) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, *9*, 1077–1080. doi:10.1246/cl.1980.1077

(24) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31–34. doi:10.1021/ol9905349

(25) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, *2000*, 236–238. doi:10.1055/s-2000-6494
(26) Tayama, E.; Tanaka, H.; Nakai, T. *Heterocycles* **2005**, *66*, 95. doi:10.3987/COM-05-S(K)39
(27) Couty, F.; Drouillat, B.; Marrot, J. *Synlett* **2009**, *5*, 767–770. doi:10.1055/s-0028-1087939
(28) Hanessian, S.; Talbot, C.; Saravanan, P. *Synthesis* **2006**, *2006*, 723–734. doi:10.1055/s-2006-926314
(29) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066–1067. doi:10.1021/ja043768i
(30) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc. Chem. Commun.* **1971**, No. 22, 1494. doi:10.1039/c29710001494
(31) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc. Perkin 1* **1980**, 1436. doi:10.1039/p19800001436
(32) Jemison, R. W.; Laird, T.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc. Perkin 1* **1980**, No. 0, 1450–1457. doi:10.1039/P19800001450
(33) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc. Chem. Commun.* **1973**, No. 18, 656. doi:10.1039/c39730000656
(34) Mageswaran, S.; Sutherland, I. O.; Ollis, W. D. *Journal of the Chemical Society, Perkin Transactions 1* **1981**, 1953–1962. doi:10.1039/P19810001953
(35) Neeson, S. J.; Stevenson, P. J. *Tetrahedron Lett.* **1988**, *29*, 3993–3996. doi:10.1016/S0040-4039(00)80402-5
(36) Burns, B.; Coates, B.; Neeson, S.; Stevenson, P. J. *Tetrahedron Lett.* **1990**, *31*, 4351–4354. doi:10.1016/S0040-4039(00)97620-2
(37) Sweeney, J. B.; Tavassoli, A.; Carter, N. B.; Hayes, J. F. *Tetrahedron* **2002**, *58*, 10113–10126. doi:10.1016/S0040-4020(02)01397-2
(38) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446–7479. doi:10.1021/acscatal.5b02070
(39) Bao, H.; Tambar, U. K. [2,3]-Rearrangements of Ammonium Zwitterions. In *Molecular Rearrangements in Organic Synthesis*; Rojas, C. M., Ed.; John Wiley & Sons, Inc: Hoboken, NJ, USA, **2015**; pp 459–496. doi:10.1002/9781118939901.ch15
(40) Blid, J.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 3159–3162. doi:10.1016/S0040-4039(03)00510-0
(41) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043–3049. doi:10.1021/jo035618g
(42) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352–9353. doi:10.1021/ja0510562
(43) Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294–1300. doi:10.1021/jo062178v
(44) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476–4479. doi:10.1021/ja500758n
(45) West, T. H.; Walden, D. M.; Taylor, J. E.; Brueckner, A. C.; Johnston, R. C.; Cheong, P. H.-Y.; Lloyd-Jones, G. C.; Smith, A. D. *J. Am. Chem. Soc.* **2017**, *139*, 4366–4375. doi:10.1021/jacs.6b11851
(46) Zhang, L.; Zhang, Z.-J.; Xiao, J.-Y.; Song, J. *Org. Lett.* **2018**, *20*, 5519–5522. doi:10.1021/acs.orglett.8b02521

(47) Wittig, G.; Döser, H.; Lorenz, I. *Justus Liebigs Ann. Chem.* **1949**, *562*, 192–205. doi:10.1002/jlac.19495620305
(48) Curtin, D. Y.; Leskowitz, S. *J. Am. Chem. Soc.* **1951**, *73*, 2630–2633. doi:10.1021/ja01150a062
(49) Hauser, C. R.; Kantor, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 1437–1441. doi:10.1021/ja01148a011
(50) Cast, J.; Stevens, T. S.; Holmes, J. *J. Chem. Soc. Resumed* **1960**, 3521. doi:10.1039/jr9600003521
(51) Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556–3558. doi:10.1021/ja00743a060
(52) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885–902. doi:10.1021/cr00075a011
(53) Mikami, K.; Nakai, T. *Synthesis* **1991**, *1991*, 594–604. doi:10.1055/s-1991-26523
(54) NakaI, T.; MikamI, K. The [2,3]-Wittig Rearrangement. In *Organic Reactions*; John Wiley & Sons, Inc., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **1994**; pp 105–209. doi:10.1002/0471264180.or046.02
(55) McNally, A.; Evans, B.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2116–2119. doi:10.1002/anie.200504301
(56) Peňaška, T.; Mojzes, M. M.; Filo, J.; Jurdáková, H.; Mečiarová, M.; Šebesta, R. *Eur. J. Org. Chem.* **2019**, *2019*, 605–610. doi:10.1002/ejoc.201801697
(57) Denmark, S. E.; Cullen, L. R. *J. Org. Chem.* **2015**, *80*, 11818–11848. doi:10.1021/acs.joc.5b01759
(58) Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. *Org. Lett.* **2016**, *18*, 1358–1361. doi:10.1021/acs.orglett.6b00291
(59) Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. *ACS Cent. Sci.* **2016**, *2*, 416–423. doi:10.1021/acscentsci.6b00125
(60) Kimm, M.; Ošeka, M.; Kaabel, S.; Metsala, A.; Järving, I.; Kanger, T. *Org. Lett.* **2019**, *21*, 4976–4980. doi:10.1021/acs.orglett.9b01495
(61) Kimm, M.; Järving, I.; Ošeka, M.; Kanger, T. *Eur. J. Org. Chem.* **2021**, *2021*, 3113–3120. doi:10.1002/ejoc.202100435
(62) Kitamura, M.; Hirokawa, Y.; Maezaki, N. *Chem. – Eur. J.* **2009**, *15*, 9911–9917. doi:10.1002/chem.200901212
(63) Kawasaki, T.; Kimachi, T. *Tetrahedron* **1999**, *55*, 6847–6862. doi:10.1016/S0040-4020(99)00338-5
(64) Tomooka, K.; Komine, N.; Nakai, T. *Chirality* **2000**, *12*, 505–509. doi:10.1002/(SICI)1520-636X(2000)12:5/6<505::AID-CHIR36>3.0.CO;2-3
(65) Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. *J. Org. Chem.* **2017**, *82*, 2889–2897. doi:10.1021/acs.joc.6b02786
(66) Xu, X.; Zhang, J.; Dong, S.; Lin, L.; Lin, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2018**, *57*, 8734–8738. doi:10.1002/anie.201804080
(67) Xu, X.; Dong, S.; Feng, L.; Wang, S.; Liu, X.; Feng, X. *Org. Lett.* **2020**, *22*, 2692–2696. doi:10.1021/acs.orglett.0c00649
(68) Evans, D. A.; Kim, A. S. (S)-4-Benzyl-2-Oxazolidinone. In *Encyclopedia of Reagents for Organic Synthesis (EROS)*; John Wiley & Sons, Ltd, **2001**. doi:10.1002/047084289X.rb066m
(69) Kobayashi, S.; Yamashita, Y. *Acc. Chem. Res.* **2011**, *44*, 58–71. doi:10.1021/ar100101b
(70) Horgan, D. J.; Stoops, J. K.; Webb, E. C.; Zerner, B. *Biochemistry* **1969**, *8*, 2000–2006. doi:10.1021/bi00833a033

(71) Hilterhaus, L.; Goetz, K.; Liese, A. Enzyme Catalysis in Organic Synthesis, Third Edition; John Wiley & Sons, Inc., **2012**; pp 249–362. doi:10.1002/9783527639861.ch29
(72) Home | Sustainable Development https://sdgs.un.org/ (accessed Sep 8, 2023)
(73) Xiang, S.-H.; Tan, B. *Nat. Commun.* **2020**, *11*, 3786. doi:10.1038/s41467-020-17580-z
(74) The Nobel Prize in Chemistry 2021 https://www.nobelprize.org/prizes/chemistry/2021/summary/ (accessed Sep 18, 2023)
(75) Rajesh Krishnan, G.; Sreekumar, K. Chapter 14 - Supported and Reusable Organocatalysts. In *New and Future Developments in Catalysis*; Suib, S. L., Ed.; Elsevier: Amsterdam, **2013**; pp 343–364. doi:10.1016/B978-0-444-53876-5.00016-7
(76) Aukland, M. H.; List, B. *Pure Appl. Chem.* **2021**, *93*, 1371–1381. doi:10.1515/pac-2021-0501
(77) Said, R. B.; Kolle, J. M.; Essalah, K.; Tangour, B.; Sayari, A. *ACS Omega* **2020**, *5*, 26125–26133. doi:10.1021/acsomega.0c03727
(78) Mannisto, J. K.; Pavlovic, L.; Tiainen, T.; Nieger, M.; Sahari, A.; Hopmann, K. H.; Repo, T. *Catal. Sci. Technol.* **2021**, *11*, 6877–6886. doi:10.1039/D1CY01433A

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Abstract
Efficiency of Stereoselective [2,3]-Sigmatropic Rearrangement Reactions

The widespread trend of heightened environmental awareness and global challenges dictates the path forward for all disciplines, including chemistry. It demands alignment with the broader pursuit of sustainability, thereby shifting to more responsible and eco-conscious scientific endeavours. The general tendency is to improve existing processes, develop innovative solutions and adopt sustainable practices. This requirement extends not only to the creation of more environmentally friendly materials and chemicals but also to the optimisation of processes, the reduction of waste, and the incorporation of renewable resources.

The primary focus of this thesis has been to enhance the utility of [2,3]-sigmatropic rearrangement reactions, thereby potentially contributing to the ongoing challenges of sustainable and efficient chemistry. To start with, a stereoselective [2,3]-sigmatropic rearrangement of *N*-ammonium ylides was investigated. Various electron-withdrawing groups were screened, revealing that the inclusion of the oxazolidinyl moiety substantially increased the diastereoselectivity of the reaction (up to 15.7:1). Through further optimisation, a suitable base was identified, significantly reducing the reaction time to less than one minute.

Another significant contribution involved the development of an efficient one-pot method, integrating an asymmetric Ca^{2+}-catalysed [2,3]-Wittig rearrangement reaction with enzymatic desymmetrisation of malonic esters. This one-pot approach was versatile for synthesising α-hydroxy half-esters with vicinal quaternary and tertiary stereogenic centres. Notably, various α-branched sterically demanding esters were tolerated, streamlining the synthetic pathway without needing intermediate isolation and providing products with ee_{maj} up to 81% and ee_{min} up to 99%.

Finally, acknowledging the increasing transition from the traditional linear approach of reactions (take, use and dispose) to a more sustainable circular approach (make, use and return), this thesis also addresses the recyclability of organocatalysts. A range of polystyrene-supported enantiomerically pure aminocatalysts were prepared for this purpose. The utilisation of amino acids anchored to (aminomethylated)polystyrene proved particularly effective in asymmetric [2,3]-Wittig rearrangement reactions of cyclohexanone derivatives. Through a simplified isolation procedure involving only filtration and washing steps, a model rearranged product was obtained in high yield (84%) and enantioselectivities (ee_{maj} 86%, ee_{min} 86%). Importantly, it was observed during optimisation that the end-capping of the heterogeneous catalysts plays a significant role in their reusability. Catalysts prepared with bulkier pivaloyl end-capping moieties exhibited exceptional recyclability, lasting up to six cycles without significant deactivation.

Lühikokkuvõte
Stereoselektiivsete [2,3]-sigmatroopsete ümberasetusreaktsioonide efektiivsus

Suurenenud keskkonnateadlikkus ning globaalsed väljakutsed määravad edasised arengusuunad kõigile teadusharudele, sealhulgas ka keemiale. Üldine suund jätkusuutlikkuse poole suunab ka teadust vastutustundlikumatele ja keskkonnateadlikumatele tegevustele. Seeläbi soovitakse parandada olemasolevaid protsesse, arendada innovaatilisi lahendusi ja võtta kasutusele jätkusuutlikud praktikad. See nõue ei laiene mitte ainult keskkonnasõbralikumate materjalide ja kemikaalide loomisele, vaid ka protsesside optimeerimisele, jäätmete vähendamisele ja taastuvate ressursside kaasamisele.

Doktoritöö peamine eesmärk on aidata kaasa jätkusuutliku keemia arengule [2,3]-sigmatroopsete ümberasetusreaktsioonide väärtustamise kaudu. Kõigepealt, uuriti *N*-ammooniumüliidide stereoselektiivset [2,3]-sigmatroopset ümberasetusreaktsiooni. Erinevate elektronaktseptoorsete rühmade kasutamisel selgus, et oksasolidinüülrühma lisamine suurendas märkimisväärselt reaktsiooni diastereoselektiivsust (*dr* kuni 15,7:1). Edasise optimeerimise käigus leiti sobiv alus, mis vähendas oluliselt reaktsiooniaega viies selle alla ühe minuti.

Järgmisena keskenduti efektiivse "ühe-kolvi" meetodi väljatöötamisele, ühendades asümmeetrilise Ca^{2+}-katalüütilise [2,3]-Wittigi ümberasetusreaktsiooni maloonestrite ensümaatilise desümmetriseerimisega. Antud "ühe-kolvi" lähenemine võimaldas sünteesida α-hüdroksüpoolestreid, mis sisaldavad vitsinaalseid kvaternaarseid ja tertsiaarseid stereogeenseid tsentreid. Reaktsioonis kasutati erinevaid α-asendatud steeriliselt mahukaid estreid ilma vaheühendi eraldamiseta. Reaktsiooni tulemusel saadi produktid kõrge enantiomeerse puhtusega (ee_{maj} kuni 81% ja ee_{min} kuni 99%).

Teadvustades traditsioonilise lineaarse majandusmudeli (võta, tarbi, viska minema) ebatõhusust jätkusuutlikkuse seisukohast ning kasvavat üleminekut ringmajandusele (tooda, tarbi, taaskasuta), käsitleb see doktoritöö ka organokatalüsaatorite taaskasutamise aspekti. Selleks valmistati erinevaid polüstüreenile seotud enantiomeerselt puhtaid aminokatalüsaatoreid. Aminohapete kasutamine, mis olid seotud (aminometüüleeritud)polüstüreenile, osutus eriti tõhusaks asümmeetrilistes [2,3]-Wittigi ümberasetusreaktsioonides tsükloheksanooni derivaatidega. Lihtsustatud eraldamisprotseduuri abil, mis hõlmas ainult filtreerimist ja pesemist, saadi produkt kõrge saagise (84%) ja enantiomeerse puhtusega (ee_{maj} 86%, ee_{min} 86%). Leiti, et oluliseks sammuks korduvkasutatavuse saavutamiseks on katalüsaatori kandjal reageerimata jäänud aminorühmade kaitsmine. Katalüsaatoreid, mille vabad aminorühmad olid blokeeritud mahukama pivaloüülrühmaga, oli võimalik taaskasutada kuni kuus korda ilma nende olulise deaktiveerumiseta.

Appendix 1

Publication I

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Synthesis A. Murre et al. Paper

Diastereoselective [2,3]-Sigmatropic Rearrangement of *N*-Allyl Ammonium Ylides

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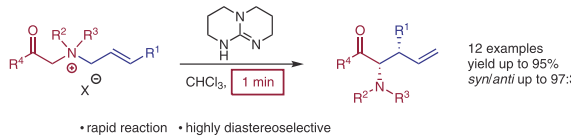

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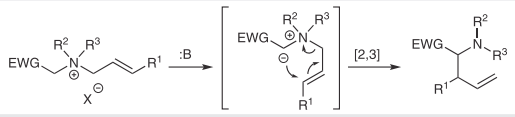
Abstract A rapid and diastereoselective method was developed for the [2,3]-sigmatropic rearrangement of *N*-allyl ammonium ylides, affording products in up to 95% isolated yields and up to 97:3 dr; most of the desired products were formed within 1 minute. For the asymmetric reaction, a chiral auxiliary was introduced to the starting compound, affording the rearrangement product with high diastereoselectivities.

Key words [2,3]-sigmatropic rearrangement, ammonium ylide, auxiliary, diastereoselectivity, oxazolidinyl group, α-amino ketones

Pericyclic reactions are considered to be one of the most useful organic reactions, as they give access to the formation of several new C–C or C–heteroatom bonds in a single step in 100% atom efficiency. The rearrangement of allylic or propargylic ethers (Wittig rearrangement) is one of the most studied of this type of reaction, as it can provide homoallyl alcohols in an enantioselective manner.[2] We have previously investigated the enantioselective [2,3]-Wittig rearrangement of oxindoles[3] and allyloxymalonates.[4] Contrary to a [2,3]-Wittig rearrangement reaction, its aza-analogue can only be performed under superbasic conditions,[5] with strained ring systems[6] or by inserting an alkylsilyl group on the allyl chain of the starting compound.[7] Unactivated acyclic amino compounds do not readily undergo [2,3]-rearrangement reactions. This problem can be bypassed by the quaternization of the tertiary amino group. Ammonium salts can be formed either by in situ quaternization or by alkylation. Alternatively, tertiary amine can be activated by Lewis acids, followed by the subsequent rearrangement reaction.[8–10]

The [1,2]-Stevens rearrangement and [2,3]-sigmatropic rearrangement of amines are transformations, in which, after quaternization, the ammonium ylide is generated either in situ or as an isolated intermediate (Scheme 1).[2b,11,12] Subsequently, the migration of the allyl group occurs, followed by the formation of a new C–C bond. In the case of substitution at the allylic position, the [2,3]-rearrangement leads to the formation of diastereomers. [1,2]- and [2,3]-Rearrangements are competitive with each other, but can be directed towards the desired reaction pathway by selecting suitable reaction conditions. In the rearrangement of *N*-benzylic ammonium ylides, a Sommelet–Hauser rearrangement can compete with [1,2]-Stevens reaction.[13]



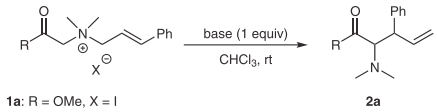
Scheme 1 [2,3]-Rearrangement of *N*-allylic ammonium ylides

If the electron-withdrawing group is a carboxylic acid derivative, the [2,3]-rearrangement of *N*-allylic ammonium ylides affords homoallylic tertiary amines, which can also be considered to be α-amino acid derivatives. Often a rearrangement reaction occurs spontaneously after the ammonium ylides are formed. This makes performing Stevens rearrangement diastereoselectively challenging. The [2,3]-rearrangement of allylic ammonium ylides was initially studied by Ollis and Jemison.[14] Tambar and Soheili have shown that high diastereoselectivities were achieved through tandem Pd-catalytic amination, followed by [2,3]-sigmatropic rearrangement.[15] The stereoselectivity of the forming product can also be induced by chiral catalysts or auxiliaries, or through chirality transfer.[16–20] Somfai and co-workers have developed a stoichiometric asymmetric rearrangement reaction using Lewis acids to generate products with excellent enantioselectivities and diastereoselectivities.[10a,21] Sweeney and co-workers have utilized chiral

auxiliary control with camphorsultams, producing the rearranged products in excellent selectivities.[22] Up to now, only one catalytic asymmetric method has been developed by Smith and co-workers to achieve enantiomerically pure rearrangement products.[23]

To the best of our knowledge, systematic studies of diastereoselective base-catalyzed [2,3]-sigmatropic rearrangement reactions are mostly based on cyclic ammonium ylides[24] rather than acyclic ones.

Herein we present the results of the base-induced [2,3]-rearrangement of acyclic *N*-allylic ammonium ylides utilizing steric hindrance of the electron-withdrawing group to achieve a diastereoselective outcome (Scheme 2).



1a: R = OMe, X = I
1b: R = oxazolidinyl, X = Br

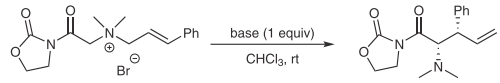
2a
2b

Scheme 2 [2,3]-Sigmatropic rearrangement of *N*-cinnamyl ammonium salts

Our preliminary experiments with cinnamyl-substituted methyl ester derivative **1a** showed that the use of methyl ester as an electron-withdrawing group (EWG) gave poor results. In 24 hours no reaction was observed in the presence of DIPEA, with DBU 84% conversion was reached within 2 hours, but the diastereoselectivity was only 40:60 (*syn*/*anti*). On that note, the ester moiety was replaced with a bulkier and stronger EWG group, oxazolidinyl, to influence both the reactivity of the substrate and the selectivity of the reaction. Subsequently, reaction conditions were screened with this more active starting compound (Table 1).

First, several organic bases were screened for the reaction. There was a clear correlation between the basicity of the used base and the reaction time. With weaker bases (imidazole, DABCO, and DMAP) only up to 46% conversion was obtained in 24 hours (Table 1, entries 1–3). In the case of imidazole, the diastereomeric ratio of the products was not determined, but for DABCO and DMAP, it was equally high. Tertiary amines Et_3N and DIPEA gave even higher diastereoselectivity in 24 hours (Table 1, entries 4 and 5). In terms of selectivity and reaction time, stronger bases, such as DBU and TBD, were equal, giving the rearranged product almost instantly. To determine the reaction time, a sample from the reaction mixture was quenched with acetic acid when the mixture turned from heterogeneous to homogeneous. ^{1}H NMR of the crude reaction mixture showed only the rearranged product after 1 minute (Table 1, entries 6 and 7). Since the reaction with the aforementioned bases was rapid, the reaction in the presence of TBD was also conducted at –45 °C (Table 1, entry 8). The diastereoselectivity rose from 93:7 to 97:3, but the reaction time increased to 2 hours. In the presence of *t*-BuOK the conversion remained

Table 1 Screening of the Reaction Conditions[a]



1b **2b**

Entry	Base (1 equiv)	Time	Conversion (%)[b]	Ratio *syn*/*anti*[c]
1	imidazole	24 h	12	–[d]
2	DABCO	24 h	46	92:8
3	DMAP	24 h	28	92:8
4	Et_3N	24 h	100	93:7
5	DIPEA	24 h	100	93:7
6	DBU	1 min	100	92:8
7	TBD[e]	1 min	100	93:7
8[f]	TBD	2 h	100	97:3
9	*t*-BuOK	24 h	34	94:6
10	$NaHCO_3$	72 h	34	80:20
11	K_2CO_3	24 h	25	86:14
12	Cs_2CO_3	2 h	90	89:11
13	$K_3PO_4{\cdot}H_2O$	24 h	4	–[d]
14	K_2HPO_4	24 h	22	92:8

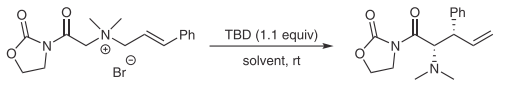
[a] Reaction conditions: **1b** (0.05 mmol), base (0.05 mmol), $CHCl_3$ (200 μL), rt, stirring.
[b] Conversion was determined by ^{1}H NMR of the crude product.
[c] Diastereomeric ratio was determined by ^{1}H NMR of the crude product; the major diastereomer is depicted in the scheme.
[d] Not determined.
[e] TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[f] Reaction was carried out at –45 °C.

low (34%) after 24 hours, due to the poor solubility of the base in $CHCl_3$ (Table 1, entry 9). The reaction with inorganic bases turned out to be less selective or slower (Table 1, entries 10–14) than with organic bases. More suitable solvents for inorganic bases (e.g. alcohols, water) could not be selected, as they would act as nucleophiles toward the oxazolidinone ring, resulting in its opening. No [1,2]-rearranged product was determined in the screening study. Based on the obtained results, TBD was chosen as the superior base as it gave the product in a high diastereomeric ratio in a very rapid reaction (reaction time only 1 minute). Next, a variety of solvents were screened.

In other chlorinated solvents, the rearrangement reaction was also complete within 1 minute (Table 2, entries 2 and 3), but the diastereoselectivity dropped compared to chloroform (Table 2, entry 1). The reaction was significantly slower in other organic solvents (Table 2, entries 4–6). As a result, the scope of the reaction was evaluated using TBD in chloroform (Scheme 3).

First we screened the influence of electron-withdrawing groups, starting from methyl ester **1a**. Under the optimal conditions, the reaction was completed in 1 minute, but the

Table 2 Screening of Different Solvents[a]

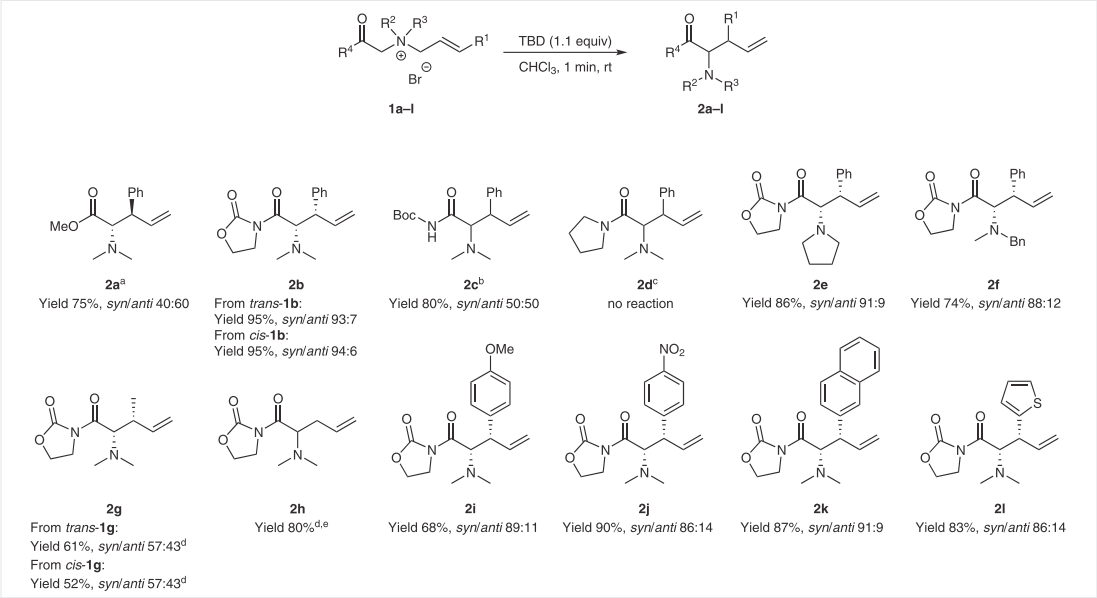


1b **2b**

Entry	Solvent	Time	Conversion (%)[b]	Ratio *syn*/*anti*[c]
1	$CHCl_3$	1 min	100	93:7
2	CH_2Cl_2	1 min	100	87:13
3	DCE	1 min	100	86:14
4	DMSO	1 h	83	82:18
5	toluene	1 h	79	86:14
6	THF	1 h	82	82:18

[a] Reaction conditions: **1b** (0.05 mmol), TBD (0.05 mmol), solvent (200 μL), rt, stirring.
[b] Conversion was determined by ^{1}H NMR of the crude product.
[c] Diastereomeric ratio was determined by ^{1}H NMR of the crude product; the major diastereomer is depicted in the scheme.

diastereoselectivity of product **2a** remained low (*syn*/*anti* 40:60). In the case of oxazolidinyl derivative **1b**, both geometric isomers *trans*-**1b** and *cis*-**1b** were equally reactive and afforded rearranged products in high yields and diastereoselectivities. In either case, the preferred diastereomer of **2b** was in *syn*-configuration, indicating that the product from *trans*-**1b** was formed through an *endo* transition state and the product from *cis*-**1b** through an *exo* transition state. When the EWG was changed to a Boc-protected amide (compound **1c**), two equivalents of base were required as the nitrogen atom in the amide moiety was also deprotonated by TBD. The yield of the product **2c** remained high (80%), but the diastereoselectivity was 50:50 as determined by ^{1}H and ^{13}C NMR. The 50:50 ratio of diastereomers was caused by enolization, which was additionally confirmed by IR analysis (see Supporting Information). Amide **1d** with the weakest electron-withdrawing group gave no reaction either at room temperature or at elevated temperature. The obtained results revealed that the diastereoselectivity of the rearrangement reaction could be easily directed towards the formation of the *syn*-product by using the oxazolidinyl group as the EWG. Next, we investigated the influence of the nitrogen atom substituents on the selectivity of the reaction. Pyrrolidinyl and benzyl(methyl)amino-substituted starting compounds afforded the products **2e** and **2f** in good yields and diastereoselectivities: 86% (dr 91:9) and 74% (dr 88:12), respectively. When the *N*-cinnamyl substituent was replaced with either *N*-crotyl or *N*-allyl group (**1g** and **1h**, respectively), the starting compounds were extremely moisture sensitive. While the reactions were conducted under typical reaction conditions, mainly the

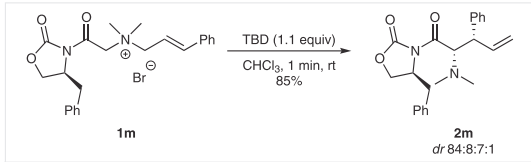


Scheme 3 Scope of the reaction. *Reagents and conditions*: **1a–l** (1 equiv), TBD (1.1 equiv), $CHCl_3$ (0.25 M solution), rt, stirring, 1 min; isolated yields are given. Diastereomeric ratio was determined by ^{1}H NMR of the crude product. Major diastereomers are depicted in the scheme. [a] Starting from the iodide salt of **1a**. [b] TBD (2 equiv), stirring, 30 min. [c] rt and 60 °C, 24 h. [d] Under Ar atmosphere with added molecular sieves (4 Å). [e] The purity of the product was 94%. The main impurity was oxazolidin-2-one, which has the same R_f value as compound **2h**.

formation of hydrolysis products of starting materials **1g** and **1h** (carboxylic acid and oxazolidin-2-one) was observed. It is assumed that in the case of *N*-cinnamyl-substituted starting compounds the phenyl ring shields the carbonyl group of the amide moiety and no nucleophilic side reaction is observed. Subsequently, the reactions were conducted under anhydrous conditions, resulting in product **2g** from *trans*-**1g** in 61% yield and 57:43 diastereoselectivity, and in product **2h** in 80% yield. When a crotyl derivative *cis*-**1g** was used as a starting compound, similar results to *trans*-**1g** were obtained, which showed that the presence of the phenyl ring in the starting compound was essential in order to favor one transition state and, consequently, high diastereoselectivity. Finally, the aromatic substitution effects were evaluated. The rearrangement reaction was not dependent on the electron density of the aromatic ring and both the electron-donating methoxy and the electron-withdrawing nitro group containing starting compounds **1i** and **1j** and naphthyl- and heteroaromatic thienyl-substituted ammonium salts **1k** and **1l** gave the desired products **2i–l** in high yields and dr values.

Since product **2c** was epimerized, causing a 50:50 ratio of diastereomers, additional epimerization studies were conducted with products **2a**, **2b**, **2i**, and **2k**. The experiments revealed that no epimerization occurred with any of the compounds under the reaction conditions.

In order to evaluate possible enantioselective outcome, a chiral auxiliary based approach utilizing (*S*)-4-benzyloxazolidin-2-one in the synthesis of the ammonium salt **1m** was studied (Scheme 4). Under the optimized conditions, the product **2m** was generated in 1 minute with a diastereomeric ratio of 84:8:7:1. The dr of the two *syn*-diastereomers is 84:8 or larger (84:7 or 84:1) which corresponds to at least 83% de. After removal of the auxiliary the *syn*-diastereomer should thus exhibit an enantiopurity of at least 83% ee.



Scheme 4 Auxiliary based [2,3]-sigmatropic rearrangement

The obtained results indicated that both oxazolidinyl and cinnamyl substituents in the starting compound are essential to achieve a high diastereoselectivity of the reaction. The relative *syn*-configuration of the product was determined by a single crystal X-ray structure analysis of compound **2i** (Figure 1a). According to these data, a possible transition state model (Figure 1b) can be proposed to explain the origin of high diastereoselectivity. The ratio of diastereomers was determined by the differences in energies between *endo*- and *exo*-transition states.[25] In the case of the *trans*-substituted double bond, the *endo* cyclic transition state led to the formation of the *syn*-product and the *exo* cyclic to the *anti*-product. The stacking between the phenyl ring and carbonyl group of the oxazolidinyl ring stabilized the *endo*-transition state, affording major diastereomer **2i** with *syn*-configuration. The substituents in the phenyl ring did not weaken the interaction between the phenyl ring and carbonyl group. The fact that starting compounds with an electron-rich and electron-poor phenyl ring (**1i** and **1j**, respectively) led to similar diastereoselectivities revealed that other factors should be also considered. The diastereoselectivity dropped drastically if the oxazolidinyl group was changed to the methoxy group (compound **2a**) or the vinylic aromatic ring was substituted for the methyl group

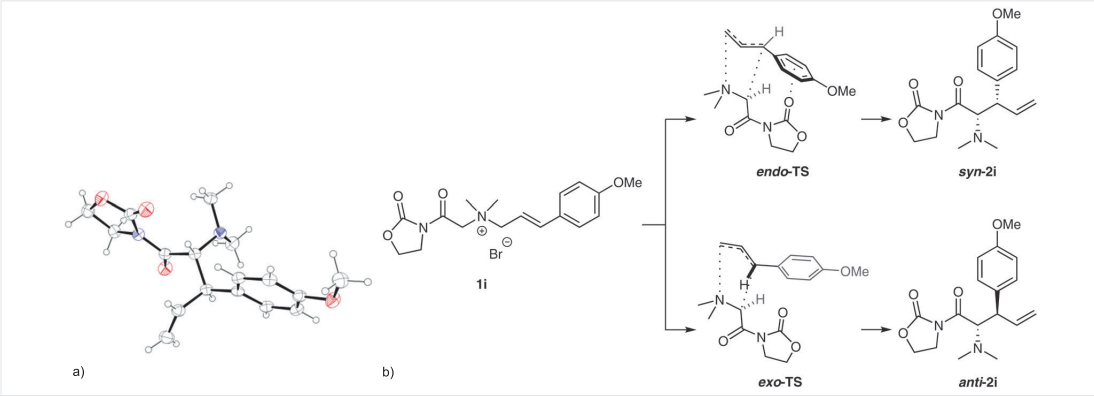


Figure 1 (a) Crystal structure of the major diastereomer of **2i**, showing only the (*R*,*R*)-enantiomer of the racemic *syn*-product. The anisotropic displacement ellipsoids are drawn at 50% probability level. (b) The proposed transition states for *N*-allylic ammonium ylide **1i**.

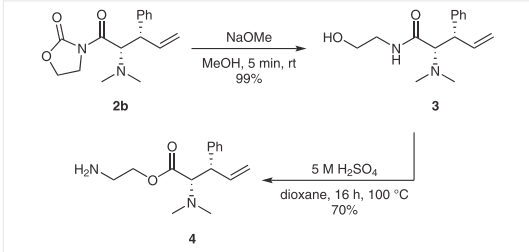
(compound **2g**). If either the oxazolidinyl or an aromatic moiety was absent from the structure, neither of the transition states was favored and diastereomers were formed in almost 1:1 ratio. It is assumed that in the case of *cis*-substituted double bond the reaction goes through an *exo*-transition state, leading to *syn*-products. In this case there are also possible interactions between the phenyl and oxazolidinyl rings.

The removal of the oxazolidinyl group from a bulky substrate in order to achieve carboxylic acid derivatives or alcohols has posed a problem[26] since the introduction of these types of auxiliaries. In general, there are two competitive reaction centers. In the case of the cleavage of the acyclic amide bond, an exocyclic cleavage product is formed. Alternatively, the reaction may occur via attack on the carbonyl group of the oxazolidinone ring, affording an endocyclic cleavage product.

Several attempts with numerous methods were made to cleave or reduce the oxazolidinyl group from compounds **2** (see Supporting Information). Firstly, the most commonly used method involving hydrolysis with $LiOH/H_2O_2$[27] afforded a mixture of different endocyclic cleavage products. Reduction with various hydrides[28] ($NaBH_4$, $LiBH_4$, $LiAlH_4$) at different temperatures (–40 °C to rt) in the presence or absence of various Lewis acids (I_2, $BF_3{\cdot}Et_2O$, BEt_3) gave a mixture of products. The reduction of **2b** with $NaBH_4$ in THF/H_2O provided the products in 66:34 ratio (respectively, *exo*- and *endo*-product). Although full conversion was achieved, the obtained products were inseparable by column chromatography. A recently published method utilizing $Yb(OTf)_3$[29,30] afforded mainly the endocyclic cleavage product. SmI_2 catalysis[31] led to the endocyclic cleavage product which reacted further giving a primary alcohol; additionally, the elimination of tertiary amine occurred. The removal of oxazolidin-2-one in the methoxide–dimethyl carbonate system affording methyl esters has been reported by Kanomata and co-workers.[32] In our case the method did not give the expected product, endocyclic cleavage product and its derivative were formed instead. It is assumed that substituents at the α-position of the carbonyl group shielded the exocyclic cleavage, providing preferably the endocyclic cleavage product.

In the presence of NaOMe in methanol, only the endocyclic cleavage product **3** was obtained in 99% yield (Scheme 5). When the obtained amide **3** was submitted to hydrolysis, a nucleophilic attack by the side chain hydroxyl group on the amide bond occurred, followed by an N–O acyl shift,[33] affording the desired amino ester **4** in 70% yield.

We have described a highly diastereoselective [2,3]-sigmatropic rearrangement of *N*-allyl ammonium ylides. The reaction is very fast, leading to full conversion of the starting material within 1 minute. The diastereoselectivity of the reaction was greatly influenced by the presence of an aromatic substituent on the allyl moiety and the oxazolidinyl group in the electron-withdrawing part of the starting compound. In the chiral auxiliary based approach obtained high dr value indicates at least 83% ee for the major diastereomer. Further insight into the enantioselective [2,3]-sigmatropic rearrangement reaction will be taken in the future. The removal of the oxazolidinyl group was achieved through endocyclic cleavage, followed by an N–O acyl shift, affording amino ester in 69% overall yield.



Scheme 5 The removal of oxazolidinyl group from compound **2b**

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 (^1H NMR), 77.16 (^{13}C NMR) and DMSO-d_6 δ = 2.50 (^1H NMR), 39.52 (^{13}C NMR)] as internal standards. All peak assignments are confirmed by 2D experiments (^1H-^1H COSY, ^1H-^{13}C HSQC, ^1H-^{13}C HMBC). In ^{13}C NMR, 2 C in brackets refers to either two chemically equivalent or two overlapping unique carbon signals. For the determination of diastereomeric ratio, CH integrals of the double bonds were used. If possible, the obtained ratio of diastereomers was also checked using the COCH or $N(CH_3)_2$ integrals. HRMS were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. Optical rotations were obtained on an Anton Paar GWB Polarimeter MCP500 at 21 °C in $CHCl_3$ and calibrated with pure solvent as a blank. Precoated silica gel plates (Merck 60 F254) were used for TLC. Column chromatography was performed on a Biotage Isolera Prime preparative purification system with silica gel Kieselgel 63–200 μm. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. Petroleum ether has bp 40–60 °C. The reactions were performed under an air atmosphere without additional moisture elimination unless stated otherwise.

Synthesis of Starting Materials 1a–l

The synthesis of ammonium salts **1a–l** was achieved as follows: amines were alkylated with unsaturated halides, which were then submitted to quaternization, affording the desired compounds **1**.

Tertiary Amines; General Procedure A (GPA)

Method A: To a solution of unsaturated chloride (1 equiv) in abs EtOH (1 M solution) was added NaI (0.2 equiv) and the mixture was stirred for 5 min at rt Then, secondary amine (5 equiv) was added and the mixture was stirred until the reaction was complete (TLC or ^1H NMR). The mixture was concentrated and the crude mixture was purified by column chromatography (silica gel).

Method B: To a solution of $Me_2NH{\cdot}HCl$ (2 equiv) in water (6 M solution) cooled to 0 °C was added NaOH (4 equiv) in portions. Then unsaturated halide (1 equiv) was added dropwise. The mixture was stirred at 0 °C until the reaction was complete (^1H NMR). The organic layer was separated, dried (NaOH), and filtered. The crude product was purified by distillation.

Method C: To a solution of unsaturated halide (1 equiv) in MeCN (0.5 M solution) was added secondary amine (2 equiv) and K_2CO_3 (1.5 equiv). The mixture was stirred at rt until the reaction was complete (TLC or ^1H NMR). The mixture was concentrated and the crude mixture was purified by column chromatography (silica gel) or by distillation.

(*E*)-*N*,*N*-Dimethyl-3-phenylprop-2-en-1-amine

Following GPA, method A, starting from (*E*)-(3-chloroprop-1-enyl)benzene (391 mg, 2.57 mmol) and Me_2NH (6.423 mL, 12.85 mmol, 2 M solution in THF), the mixture was stirred for 22 h. Purification by column chromatography (2% $MeOH/NH_3$ in CH_2Cl_2) gave the product (410 mg, 99%) as a yellow amorphous solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 2 H, Ar), 7.34–7.28 (m, 2 H, Ar), 7.26–719 (m, 1 H, Ar), 6.52 (d, *J* = 15.9 Hz, 1 H, ArC*H*), 6.27 (dt, *J* = 15.9, 6.7 Hz, 1 H, C*H*CH_2), 3.08 (dd, *J* = 6.7, 1.2 Hz, 2 H, CH_2), 2.28 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.1, 132.5, 128.6 (2 C), 127.48, 127.42, 126.3 (2 C), 62.1, 45.3 (2 C).

Analytical data are in agreement with the literature data.[23a]

***N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine**

Following GPA, method C, starting from (3-chloroprop-1-ynyl)benzene (690 mg, 4.58 mmol) and Me_2NH (4.582 mL, 9.16 mmol, 2 M solution in THF), the mixture was stirred for 2 h. Purification by column chromatography (1–2% $MeOH/NH_3$ in CH_2Cl_2) gave the product (467 mg, 59%) as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.40 (m, 2 H, Ar), 7.33–7.27 (m, 3 H, Ar), 3.47 (s, 2 H, CH_2), 2.37 (s, 6 H, $N(CH_3)_2$).

Analytical data are in agreement with the literature data.[23a]

1-Cinnamylpyrrolidine

Following GPA, method A, starting from (*E*)-(3-chloroprop-1-enyl)benzene (100 mg, 0.66 mmol) and pyrrolidine (274 μL, 3.29 mmol), the mixture was stirred for 21 h. Purification by column chromatography (2–5% $MeOH/NH_3$ in CH_2Cl_2) gave the product (105 mg, 85%) as a pale yellow amorphous solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 2 H, Ar), 7.35–7.26 (m, 2 H, Ar), 7.25–7.18 (m, 1 H, Ar), 6.54 (d, *J* = 15.8 Hz, 1 H, ArC*H*), 6.34 (dt, *J* = 15.8, 6.7 Hz, 1 H, C*H*CH_2), 3.27 (dd, *J* = 6.7, 1.3 Hz, 2 H, CHCH_2), 2.62–2.48 (m, 4 H, $N(CH_2)_2$), 1.89–1.73 (m, 4 H, $(CH_2)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 131.8, 128.5 (2 C), 127.8, 127.3, 126.3 (2 C), 58.5, 54.1 (2 C), 23.5 (2 C).

Analytical data are in agreement with the literature data.[34]

(*E*)-*N*,*N*-Dimethylbut-2-en-1-amine

Following GPA, method B, starting from commercial (*E*)-1-chlorobut-2-ene (*cis*/*trans* (*Z*/*E*) mixture 15:85, 5 g, 55.22 mmol) and $Me_2NH{\cdot}HCl$ (9.005 g, 110.44 mmol), the mixture was stirred for 2 h. Distillation gave the product (1.538 g, 30%) as a colorless liquid; bp 90–93 °C; *cis*/*trans* (*Z*/*E*) mixture 15:85.

(*E*)-*N*,*N*-Dimethylbut-2-en-1-amine

^1H NMR (400 MHz, $CDCl_3$): δ = 5.64–5.52 (m, 1 H, CH), 5.52–5.41 (m, 1 H, CH), 2.81 (d, *J* = 6.5 Hz, 2 H, CH_2), 2.18 (s, 6 H, $N(CH_3)_2$), 1.68 (dd, *J* = 6.1, 1.1 Hz, 3 H, CH_3).

Analytical data are in agreement with the literature data.[35]

(*Z*)-*N*,*N*-Dimethylbut-2-en-1-amine

^1H NMR (400 MHz, $CDCl_3$): δ = 5.64–5.52 (m, 1 H, CH), 5.52–5.41 (m, 1 H, CH), 2.92 (d, *J* = 6.9 Hz, 2 H, CH_2), 2.21 (s, 6 H, $N(CH_3)_2$), 1.65–1.61 (m, 3 H, CH_3).

***N*,*N*-Dimethylbut-2-yn-1-amine**

Following GPA, method B, starting from 1-bromobut-2-yne (3.418 g, 25.70 mmol) and $Me_2NH{\cdot}HCl$ (4.191 g, 51.40 mmol), the mixture was stirred for 30 min. Distillation gave the product (1.937 g, 78%) as a colorless liquid; bp 90–92 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.15 (q, *J* = 2.3 Hz, 2 H, CH_2), 2.27 (s, 6 H, $N(CH_3)_2$), 1.83 (t, *J* = 2.4 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 80.4, 74.1, 48.1, 44.1, 3.3.

Analytical data are in agreement with the literature data.[36]

(*E*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine

Following GPA, method A, starting from (*E*)-1-(3-chloroprop-1-enyl)-4-methoxybenzene (263 mg, 1.44 mmol) and Me_2NH (3.560 mL, 7.20 mmol, 2 M solution in THF), the mixture was stirred for 2 h. Purification by column chromatography (1–4% $MeOH/NH_3$ in CH_2Cl_2) gave the product (131 mg, 48%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 2 H, Ar), 6.89–6.81 (m, 2 H, Ar), 6.45 (d, *J* = 15.8 Hz, 1 H, ArC*H*), 6.12 (dt, *J* = 15.8, 6.8 Hz, 1 H, C*H*CH_2), 3.80 (s, 3 H, OCH_3), 3.05 (dd, *J* = 6.8, 1.2 Hz, 2 H, CH_2), 2.27 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 132.0, 129.9, 127.5 (2 C), 125.2, 114.0 (2 C), 62.2, 55.3, 45.3 (2 C).

Analytical data are in agreement with the literature data.[23a]

(*E*)-*N*,*N*-Dimethyl-3-(4-nitrophenyl)prop-2-en-1-amine

Following GPA, method C, starting from (*E*)-1-(3-bromoprop-1-enyl)-4-nitrobenzene (146 mg, 0.60 mmol) and Me_2NH (603 μL, 1.21 mmol, 2 M solution in THF), the mixture was stirred for 30 min. Purification by column chromatography (2–5% MeOH in CH_2Cl_2) gave the product (74 mg, 60%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.10 (m, 2 H, Ar), 7.50 (d, *J* = 8.8 Hz, 2 H, Ar), 6.60 (d, *J* = 16.1 Hz, 1 H, ArC*H*), 6.46 (dt, *J* = 15.9, 6.4 Hz, 1 H, C*H*CH_2), 3.14 (d, *J* = 5.3 Hz, 2 H, CH_2), 2.30 (s, 6 H, $N(CH_3)_2$).

Analytical data are in agreement with the literature data.[23a]

(*E*)-*N*,*N*-Dimethyl-3-(naphthalen-2-yl)prop-2-en-1-amine

Following GPA, method C, starting from (*E*)-2-(3-bromoprop-1-enyl)naphthalene (218 mg, 0.88 mmol) and Me_2NH (882 μL, 1.76 mmol, 2 M solution in THF), the mixture was stirred for 1 h. Purification by column chromatography (1–5% $MeOH/NH_3$ in CH_2Cl_2) gave the product (115 mg, 62%) as an off-white solid; mp 38–40 °C.

IR (KBr): 3055, 2971, 2940, 2853, 2813, 2769, 1455, 1366, 1019, 967, 854, 819, 795, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.76 (m, 3 H, Ar), 7.72 (s, 1 H, Ar), 7.61 (dd, *J* = 8.6, 1.7 Hz, 1 H, Ar), 7.49–7.40 (m, 2 H, Ar), 6.68 (d, *J* = 15.9 Hz, 1 H, Ar*CH*), 6.39 (dt, *J* = 15.9, 6.8 Hz, 1 H, *CH*CH_2), 3.14 (dd, *J* = 6.7, 1.3 Hz, 2 H, CH_2), 2.31 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.6, 133.6, 132.9, 132.6, 128.2, 127.9 (2 C), 127.7, 126.2, 126.1, 125.8, 123.6, 62.2, 45.4 (2 C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N$: 212.1434; found: 212.1437.

(*E*)-*N*,*N*-Dimethyl-3-(thiophen-2-yl)prop-2-en-1-amine

Following GPA, method A, starting from (*E*)-2-(3-chloroprop-1-enyl)thiophene (228 mg, 1.44 mmol) and Me_2NH (3.593 mL, 7.19 mmol, 2 M solution in THF), the mixture was stirred for 2 h. Purification by column chromatography (1–5% MeOH/NH_3 in CH_2Cl_2) gave the product (88 mg, 37%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.16 (m, 1 H, Ar), 6.98–6.89 (m, 2 H, Ar), 6.64 (d, *J* = 15.7 Hz, 1 H, Ar*CH*), 6.10 (dt, *J* = 15.7, 6.8 Hz, 1 H, *CH*CH_2), 3.04 (dd, *J* = 6.8, 1.3 Hz, 2 H, CH_2), 2.27 (s, 6 H, $N(CH_3)_2$).

Analytical data are in agreement with the literature data.[37]

Hydrogenation of Alkynamines

(*Z*)-*N*,*N*-Dimethyl-3-phenylprop-2-en-1-amine

H-cube system was charged with Lindlar CatCart column (5% Pd/$CaCO_3$/Pb) and the H_2 pressure was set to 1 bar with 75% of H_2 production. *N*,*N*-Dimethylbut-2-yn-1-amine (266 mg, 1.67 mmol) was dissolved in MeOH (53 mL) and the solution was pumped through the H-cube system twice with flow rate 1 mL/min. The collected solution was concentrated under reduced pressure and purified by column chromatography (2–5% MeOH in CH_2Cl_2) to give the product (233 mg, 87%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 2 H, Ar), 7.28–7.20 (m, 3 H, Ar), 6.56 (d, *J* = 11.8 Hz, 1 H, Ar*CH*), 5.78 (dt, *J* = 11.9, 6.4 Hz, 1 H, *CH*CH_2), 3.21 (dd, *J* = 6.4, 2.0 Hz, 2 H, CH_2), 2.25 (s, 6 H, $N(CH_3)_2$).

Analytical data are in agreement with the literature data.[23a]

(*Z*)-*N*,*N*-Dimethylbut-2-en-1-amine

H-cube system was charged with Lindlar CatCart column (5% Pd/$CaCO_3$/Pb) and the H_2 pressure was set to 1 bar with 50% of H_2 production. *N*,*N*-Dimethylbut-2-yn-1-amine (1.275 g, 13.12 mmol) was dissolved in MeOH (255 mL) and the solution was pumped through the H-cube system twice with flow rate 1 mL/min. The collected solution was acidified with aq 1 M HCl and concentrated under reduced pressure. Aq 40% NaOH solution was added to the residue, the aqueous phase was additionally saturated with NaCl and the amine layer was separated. Distillation gave the product (530 mg, 41%) as a colorless liquid; bp 60–75 °C).

(*Z*)-*N*,*N*-Dimethylbut-2-en-1-amine

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66–5.57 (m, 1 H, CH), 5.52–5.44 (m, 1 H, CH), 2.93 (d, *J* = 6.9 Hz, 2 H, CH_2), 2.22 (s, 6 H, $N(CH_3)_2$), 1.67–1.61 (m, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 127.4, 126.9, 55.7, 45.1 (2 C), 13.0.

(*E*)-*N*,*N*-Dimethylbut-2-en-1-amine

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66–5.57 (m, 1 H, CH), 5.52–5.44 (m, 1 H, CH), 2.93 (d, *J* = 6.9 Hz, 2 H, CH_2), 2.22 (s, 6 H, $N(CH_3)_2$), 1.67–1.61 (m, 3 H, CH_3).

Synthesis of Alkyl Halides

3-(2-Bromoacetyl)oxazolidin-2-one

To a suspension of NaH (293 mg, 7.32 mmol, 60% in mineral oil) in THF (5 mL) was added oxazolidin-2-one (490 mg, 5.63 mmol) under an argon atmosphere at 0 °C. The mixture was heated at reflux for 1 h, then cooled to 0 °C, followed by addition of 2-bromoacetyl bromide (515 μL, 5.91 mmol) solution in THF (600 μL). The mixture was stirred at 0 °C for 12 h, then it was diluted with EtOAc and sat. aq NH_4Cl solution was added. The aqueous phase was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and purified by column chromatography (silica gel, 30% EtOAc/petroleum ether) to give the product (764 mg, 65%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (s, 2 H, CH_2Br), 4.52–4.44 (m, 2 H, CH_2O), 4.09–4.04 (m, 2 H, CH_2N).

Analytical data are in agreement with the literature data.[38]

***tert*-Butyl (2-Bromoacetyl)carbamate**

The solution of 2-bromoacetamide (1.000 g, 7.25 mmol) in DCE (7 mL) was cooled to 0 °C. Oxalyl chloride (736 μL, 8.70 mmol) was added dropwise under an argon atmosphere and the mixture was stirred at this temperature for 10 min, then the mixture was heated at 65 °C for 2.5 h. The mixture was cooled to 0 °C and *t*-BuOH (1.386 mL, 14.50 mmol) in DCE (1.5 mL) was added. The mixture was stirred at 0 °C for 25 min, then poured into ice-cold sat. aq $NaHCO_3$ solution. The organic layer was separated and washed with sat. aq $NaHCO_3$ and water, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The obtained solid was stirred overnight in hexanes (5 mL), then filtered and dried under reduced pressure to afford the product (1.131 g, 66%) as white crystals; mp 101–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (br. s, 1 H, NH), 4.29 (s, 2 H, CH_2), 1.50 (s, 9 H, $C(CH_3)_3$).

Analytical data are in agreement with the literature data.[39]

(*S*)-4-Benzyl-3-(2-bromoacetyl)oxazolidin-2-one

The solution of (*S*)-4-benzyloxazolidin-2-one (300 mg, 1.69 mmol) in THF (8.5 mL) was cooled to –78 °C. BuLi (745 μL, 1.86 mmol, 2.5 M solution in hexane) was added dropwise under an argon atmosphere and the mixture was stirred at –78 °C for 1 h. Then, 2-bromoacetyl bromide (162 μL, 1.86 mmol) was added and the mixture was stirred at –78 °C for 30 min, the mixture was allowed to warm to rt and stirred for 16 h. Sat. aq NH_4Cl solution and water were added at 0 °C, and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and purified by column chromatography (silica gel, 5–25% EtOAc/petroleum ether) to give the product (467 mg, 92%) as a pale yellow oil.

$[\alpha]_D^{21}$ +47.1 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 3 H, Ar), 7.24–7.19 (m, 2 H, Ar), 4.74–4.66 (m, 1 H, NCH), 4.54 (d, *J* = 3.0 Hz, 2 H, CH_2Br), 4.31–4.20 (m, 2 H, OCH_2), 3.33 (dd, *J* = 13.4, 3.3 Hz, 1 H, $ArCH_2$), 2.81 (dd, *J* = 13.4, 9.5 Hz, 1 H, $ArCH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}NO_3$: 298.0073; found: 298.0078.

Analytical data are in agreement with the literature data.[40]

Ammonium Salts 1; General Procedure B (GPB)

To a solution of tertiary amine (1–1.5 equiv) in MeCN (1 M solution) was added a solution of alkyl halide (1 equiv) in MeCN (1 M solution). The mixture was stirred at rt until the reaction was complete by ^{1}H NMR. The solvent was removed under reduced pressure and the crude mixture was either used as received or purified by recrystallization or by stirring in a suitable solvent at rt or at reflux.

(*E*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]-3-phenylprop-2-en-1-aminium Bromide (*trans*-1b)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (469 mg, 2.91 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (605 mg, 2.91 mmol), the mixture was stirred for 2 h. Recrystallization (MeCN/EtOAc) gave the product (743 mg, 69%) as a white solid; mp 170–172 °C.

IR (KBr): 3007, 2972, 2942, 2868, 2789, 1781, 1679, 1638, 1475, 1453, 1390, 1367, 1269, 1215, 1204, 1112, 1041, 925, 704 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 7.62–7.56 (m, 2 H, Ar), 7.44–7.33 (m, 3 H, Ar), 6.89 (d, *J* = 15.7 Hz, 1 H, ArC*H*), 6.50 (dt, *J* = 15.4, 7.5 Hz, 1 H, C*H*CH$_2$), 4.81 (s, 2 H, COCH$_2$), 4.47 (t, *J* = 8.0 Hz, 2 H, CH$_2$O), 4.38 (d, *J* = 7.5 Hz, 2 H, CHC*H*$_2$), 3.95 (t, *J* = 8.0 Hz, 2 H, CH$_2$N), 3.33 (s, 6 H, N(CH$_3$)$_2$).

^{13}C NMR (101 MHz, DMSO): δ = 162.3, 151.2, 139.4, 133.1, 127.0, 126.6 (2 C), 125.2 (2 C), 114.1, 64.7, 61.5, 59.8, 48.7 (2 C), 40.1.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1547; found: 289.1563.

(*Z*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]-3-phenylprop-2-en-1-aminium Bromide (*cis*-1b)

Following GPB, starting from (*Z*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (126 mg, 0.78 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (163 mg, 0.78 mmol), the mixture was stirred for 2 h. Recrystallization (MeCN/EtOAc) gave the product (236 mg, 82%) as a white solid; mp 157–159 °C.

IR (KBr): 3014, 2965, 2865, 2793, 1783, 1701, 1484, 1412, 1404, 1290, 1230, 1133, 1039, 895, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 7.48–7.40 (m, 2 H, Ar), 7.40–7.33 (m, 1 H, Ar), 7.33–7.24 (m, 2 H, Ar), 7.00 (d, *J* = 11.8 Hz, 1 H, ArC*H*), 6.05 (dt, *J* = 12.3, 6.9 Hz, 1 H, C*H*CH$_2$), 4.80 (s, 2 H, COCH$_2$), 4.56 (d, *J* = 6.5 Hz, 2 H, CHC*H*$_2$), 4.46 (t, *J* = 8.0 Hz, 2 H, CH$_2$O), 3.80 (t, *J* = 8.0 Hz, 2 H, CH$_2$N), 3.27 (s, 6 H, N(CH$_3$)$_2$).

^{13}C NMR (101 MHz, DMSO): δ = 161.7, 150.8, 135.2, 132.4, 126.3 (2 C), 126.2 (2 C), 125.7, 115.7, 61.1, 59.4, 59.0, 48.7 (2 C), 39.7.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1547; found: 289.1551.

(*E*)-*N*-{2-[(*tert*-Butoxycarbonyl)amino]-2-oxoethyl}-*N*,*N*-dimethyl-3-phenylprop-2-en-1-aminium Bromide (1c)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (140 mg, 0.87 mmol) and *tert*-butyl (2-bromoacetyl)carbamate (207 mg, 0.87 mmol), the mixture was stirred for 21 h. Refluxing in hexane gave the product (347 mg, 91%) as white crystals; mp 84–88 °C.

IR (KBr): 3122, 3061, 2978, 2937, 1777, 1751, 1726, 1705, 1516, 1482, 1455, 1370, 1255, 1232, 1145, 777, 757, 744 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 10.9 (s, 1 H, NH), 7.64–7.54 (m, 2 H, Ar), 7.45–7.32 (m, 3 H, Ar), 6.86 (d, *J* = 15.6 Hz, 1 H, ArC*H*), 6.50 (dt, *J* = 15.4, 7.4 Hz, 1 H, C*H*CH$_2$), 4.49 (s, 2 H, COCH$_2$), 4.33 (d, *J* = 7.3 Hz, 2 H, CHC*H*$_2$), 3.25 (s, 6 H, N(CH$_3$)$_2$), 1.43 (s, 9 H, C(CH$_3$)$_3$).

^{13}C NMR (101 MHz, DMSO): δ = 165.6, 150.1, 141.2, 135.2, 129.0, 128.7 (2 C), 127.2 (2 C), 116.2, 81.9, 66.7, 62.3, 50.7 (2 C), 27.6 (3 C).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{27}N_2O_3$: 319.2016; found: 319.2030.

(*E*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-3-phenylprop-2-en-1-aminium Bromide (1d)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (100 mg, 0.62 mmol) and 2-bromo-1-(pyrrolidin-1-yl)ethan-1-one (119 mg, 0.62 mmol). Recrystallization (Et$_2$O/EtOAc) gave the product (125 mg, 57%) as a white solid; mp 117–119 °C.

IR (KBr): 3055, 3010, 2934, 2886, 1651, 1480, 1451, 1370, 1232, 979, 749 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50–7.41 (m, 2 H, Ar), 7.38–7.29 (m, 3 H, Ar), 7.03 (d, *J* = 15.2 Hz, 1 H, ArC*H*), 6.36–6.22 (m, 1 H, C*H*CH$_2$), 4.97 (s, 2 H, COCH$_2$), 4.88–4.74 (m, 2 H, CHCH$_2$), 3.68–3.60 (m, 2 H, CONCH$_2$), 3.57 (s, 6 H, N(CH$_3$)$_2$), 3.47–3.38 (m, 2 H, CONCH$_2$), 1.96–1.87 (m, 2 H, CH$_2$), 1.85–1.76 (m, 2 H, CH$_2$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 161.7, 144.3, 134.5, 129.7, 128.9 (2 C), 127.3 (2 C), 114.0, 67.1, 61.6, 50.8 (2 C), 46.42, 46.36, 26.0, 23.8.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{25}N_2O$: 273.1961; found: 273.1973.

1-Cinnamyl-1-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]pyrrolidin-1-ium Bromide (1e)

Following GPB, starting from 1-cinnamylpyrrolidine (99 mg, 0.53 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (110 mg, 0.53 mmol), the mixture was stirred overnight. Recrystallization (Et$_2$O/EtOAc) gave the product (169 mg, 81%) as a white solid; mp 154–155 °C.

IR (KBr): 3027, 2993, 2962, 2943, 1777, 1706, 1391, 1301, 1219, 1132, 1037, 984, 763 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.53–7.47 (m, 2 H, Ar), 7.39–7.31 (m, 3 H, Ar), 6.91 (d, *J* = 15.7 Hz, 1 H, ArC*H*), 6.41 (dt, *J* = 15.5, 7.6 Hz, 1 H, C*H*CH$_2$), 5.36 (s, 2 H, COCH$_2$), 4.55 (d, *J* = 7.7 Hz, 2 H, CHCH$_2$), 4.53–4.47 (m, 2 H, OCH$_2$), 4.29–4.19 (m, 2 H, NCH$_2$), 4.10–4.05 (m, 2 H, CONCH$_2$), 4.05–3.97 (m, 2 H, NCH$_2$), 2.43 (d, *J* = 6.9 Hz, 2 H, CH$_2$), 2.21–2.09 (m, 2 H, CH$_2$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 164.9, 153.6, 143.1, 134.6, 129.6, 128.9 (2 C), 127.4 (2 C), 115.1, 63.63 (2 C), 63.57, 63.3, 61.9, 42.6, 22.5 (2 C).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{23}N_2O_3$: 315.1703; found: 315.1708.

(*E*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]but-2-en-1-aminium Bromide (*trans*-1g)

Following GPB, starting from (*E*)-*N*,*N*-dimethylbut-2-en-1-amine (105 mg, 1.06 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (200 mg, 0.96 mmol), the mixture was stirred for 2 h. The crude product was dried under reduced pressure (295 mg, quantitative) as a yellow amorphous solid.

IR (KBr): 3015, 2970, 2948, 2916, 1778, 1704, 1476, 1417, 1390, 1300, 1226, 1122, 1038, 880, 755 cm^{-1}.

***trans*-1g**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38–6.16 (m, 1 H, CH_3CH), 5.71–5.53 (m, 1 H, $CHCH_2$), 5.31 (s, 2 H, $COCH_2$), 4.61–4.55 (m, 2 H, CH_2O), 4.52 (d, *J* = 7.6 Hz, 2 H, $CHCH_2$), 4.17–3.97 (m, 2 H, CH_2N), 3.49 (s, 6 H, $N(CH_3)_2$), 1.82 (dd, *J* = 6.8, 1.4 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 153.5, 143.0, 117.1, 66.9, 63.6, 63.4, 50.7 (2 C), 42.5, 18.5.

***cis*-1g**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38–6.16 (m, 1 H, CH_3CH), 5.71–5.53 (m, 1 H, $CHCH_2$), 5.42 (s, 2 H, $COCH_2$), 4.62–4.53 (m, 4 H, $CHCH_2$, CH_2O), 4.17–3.97 (m, 2 H, CH_2N), 3.52 (s, 6 H, $N(CH_3)_2$), 1.92–1.87 (m, 3 H, CH_3).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{19}N_2O_3$: 227.1390; found: 227.1395.

(*Z*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]but-2-en-1-aminium Bromide (*cis*-1g)

Following GPB, starting from (*Z*)-*N*,*N*-dimethylbut-2-en-1-amine (59 mg, 0.60 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (83 mg, 0.40 mmol), the mixture was stirred for 2 h. Drying under reduced pressure gave the crude product (123 mg, quantitative) as a white amorphous solid.

IR (KBr): 3015, 2970, 2922, 1779, 1704, 1477, 1417, 1390, 1298, 1227, 1122, 1038, 882, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (dq, *J* = 11.1, 7.1 Hz, 1 H, CH_3CH), 5.67–5.58 (m, 1 H, $CHCH_2$), 5.43 (s, 2 H, $COCH_2$), 4.64–4.54 (m, 4 H, $CHCH_2$, CH_2O), 4.10 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.53 (s, 6 H, $N(CH_3)_2$), 1.90 (dd, *J* = 7.1, 1.6 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6, 151.5, 138.1, 114.1, 61.7, 61.4, 59.1, 48.8 (2 C), 40.5, 12.3.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{19}N_2O_3$: 227.1390; found: 227.1392.

***N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]prop-2-en-1-aminium Bromide (1h)**

Following GPB, starting from *N*,*N*-dimethylprop-2-en-1-amine (90 mg, 1.06 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (200 mg, 0.96 mmol), the mixture was stirred for 2 h. Drying under reduced pressure gave the crude product (282 mg, quantitative) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17–5.93 (m, 1 H, NCH_2CH), 5.84–5.73 (m, 1 H, $CHCH_2$), 5.78–5.71 (m, 1 H, $CHCH_2$), 5.34 (s, 2 H, $COCH_2$), 4.68–4.49 (m, 4 H, $CHCH_2$, CH_2O), 4.19–4.00 (m, 2 H, CH_2N), 3.54 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 162.5, 151.5, 128.4, 122.5, 65.02, 61.8, 61.7, 49.2 (2 C), 40.6.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{17}N_2O_3$: 213.1234; found: 213.1237.

(*E*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]prop-2-en-1-aminium Bromide (1i)

Following GPB, starting from (*E*)-3-(4-methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine (127 mg, 0.66 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (138 mg, 0.66 mmol). The mixture was stirred for 2 h, then dried under reduced pressure. The obtained solid was stirred in EtOAc, filtered under argon, and dried under reduced pressure, to afford the product (213 mg, 80%) as an off-white amorphous solid.

IR (KBr): 3010, 2963, 2934, 2838, 1778, 1704, 1605, 1513, 1391, 1296, 1250, 1123, 1035, 883, 755 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 7.53 (d, *J* = 8.7 Hz, 2 H, Ar), 6.96 (d, *J* = 8.7 Hz, 2 H, Ar), 6.82 (d, *J* = 15.6 Hz, 1 H, ArCH), 6.33 (dt, *J* = 15.4, 7.6 Hz, 1 H, $CHCH_2$), 4.79 (s, 2 H, $COCH_2$), 4.46 (t, *J* = 8.0 Hz, 2 H, CH_2O), 4.34 (d, *J* = 7.5 Hz, 2 H, $CHCH_2$), 3.95 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.78 (s, 3 H, OCH_3), 3.27 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, DMSO): δ = 164.4, 160.0, 153.3, 141.3, 128.8 (2 C), 127.8, 114.1 (2 C), 113.3, 67.1, 63.5, 61.8, 55.3, 50.7 (2 C), 42.2.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{23}N_2O_4$: 319.1652; found: 319.1657.

(*E*)-*N*,*N*-Dimethyl-3-(4-nitrophenyl)-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]prop-2-en-1-aminium Bromide (1j)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-(4-nitrophenyl)prop-2-en-1-amine (71 mg, 0.34 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (72 mg, 0.34 mmol). The mixture was stirred for 2 h, then dried under reduced pressure. The obtained solid was stirred in EtOAc, filtered, and dried under reduced pressure, to afford the product (100 mg, 70%) as an off-white solid; mp 151–152 °C.

IR (KBr): 3061, 3032, 3008, 2923, 1792, 1714, 1599, 1516, 1474, 1343, 1289, 1186, 1107, 1023, 936, 873, 739 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 8.27 (d, *J* = 8.8 Hz, 2 H, Ar), 7.88 (d, *J* = 8.8 Hz, 2 H, Ar), 7.02 (d, *J* = 15.7 Hz, 1 H, ArCH), 6.78 (dt, *J* = 15.5, 7.4 Hz, 1 H, $CHCH_2$), 4.85 (s, 2 H, $COCH_2$), 4.55–4.46 (m, 2 H, CH_2O), 4.46–4.41 (m, 2 H, $CHCH_2$), 3.96 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.31 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, DMSO): δ = 164.3, 153.2, 147.3, 141.7, 138.8, 128.4 (2 C), 123.9 (2 C), 121.4, 66.1, 63.6, 62.1, 51.1 (2 C), 42.2.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{20}N_3O_5$: 334.1397; found: 334.1405.

(*E*)-*N*,*N*-Dimethyl-3-(naphthalen-2-yl)-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]prop-2-en-1-aminium Bromide (1k)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-(naphthalen-2-yl)prop-2-en-1-amine (114 mg, 0.54 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (112 mg, 0.54 mmol), the mixture was stirred for 1.5 h. Recrystallization (MeCN/EtOAc) gave the product (176 mg, 78%) as a white solid; mp 165–166 °C.

IR (KBr): 3050, 3010, 2954, 2920, 1780, 1704, 1386, 1300, 1219, 1127, 1036, 861, 816, 759, 702 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 8.02 (s, 1 H, Ar), 7.97–7.90 (m, 3 H, Ar), 7.89–7.83 (m, 1 H, Ar), 7.58–7.50 (m, 2 H, Ar), 7.05 (d, *J* = 15.6 Hz, 1 H, ArCH), 6.65 (dt, *J* = 15.3, 7.5 Hz, 1 H, $CHCH_2$), 4.85 (s, 2 H, $COCH_2$), 4.52–4.46 (m, 2 H, CH_2O), 4.46–4.41 (m, 2 H, $CHCH_2$), 3.96 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.32 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, DMSO): δ = 164.4, 153.3, 141.4, 133.1, 132.9, 132.7, 128.2, 128.1, 127.8, 127.6, 126.7, 126.7, 123.8, 116.7, 66.8, 63.6, 61.9, 50.8 (2 C), 42.2.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{23}N_2O_3$: 339.1703; found: 339.1714.

(*E*)-*N*,*N*-Dimethyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]-3-(thiophen-2-yl)prop-2-en-1-aminium Bromide (1l)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-(thiophen-2-yl)prop-2-en-1-amine (80 mg, 0.48 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (100 mg, 0.48 mmol). The mixture was stirred for 2 h,

EtOAc was added and the solid was filtered. Drying under reduced pressure gave the product (115 mg, 64%) as a fine white solid; mp 163–164 °C.

IR (KBr): 3088, 3010, 2959, 2914, 1779, 1761, 1709, 1638, 1390, 1302, 1226, 1133, 1037, 865, 728, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 7.60 (d, *J* = 4.9 Hz, 1 H, Ar), 7.31 (d, *J* = 3.2 Hz, 1 H, Ar), 7.14–7.09 (m, 1 H, Ar), 7.09–7.04 (m, 1 H, ArC*H*), 6.18 (dt, *J* = 15.4, 7.6 Hz, 1 H, C*H*CH_2), 4.79 (s, 2 H, $COCH_2$), 4.47 (t, *J* = 8.0 Hz, 2 H, CH_2O), 4.35 (d, *J* = 7.6 Hz, 2 H, CHCH_2), 3.95 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.26 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, DMSO): δ = 164.4, 153.3, 139.6, 134.7, 128.8, 128.0, 127.5, 114.7, 66.8, 63.6, 61.9, 50.7 (2 C), 42.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}N_2O_3S$: 295.1111; found: 295.1118.

(*S*,*E*)-*N*-[2-(4-Benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl]-*N*,*N*-dimethyl-3-phenylprop-2-en-1-aminium Bromide (1m)

Following GPB, starting from (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (54 mg, 0.34 mmol) and (*S*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (100 mg, 0.34 mmol). The mixture was stirred for 15 min, then dried under reduced pressure. The obtained solid was refluxed in EtOAc, filtered, and dried under reduced pressure to afford the product (113 mg, 73%) as an off-white solid; mp 151–153 °C.

$[\alpha]_D^{21}$ +15.2 (*c* 0.06, $CHCl_3$).

IR (KBr): 3061, 3030, 2985, 2799, 1773, 1693, 1384, 1361, 1213, 1202, 1103, 1040, 795, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.43 (m, 2 H, Ar), 7.39–7.27 (m, 5 H, Ar), 7.26–7.21 (m, 1 H, Ar), 7.21–7.14 (m, 2 H, Ar), 7.06 (d, *J* = 15.7 Hz, 1 H, ArC*H*), 6.34 (dt, *J* = 15.6, 7.7 Hz, 1 H, C*H*CH_2), 5.48 (d, *J* = 17.7 Hz, 1 H, $COCH_2$), 5.37 (d, *J* = 17.8 Hz, 1 H, $COCH_2$), 4.88–4.78 (m, 2 H, CHCH_2), 4.78–4.70 (m, 1 H, NCH), 4.51 (t, *J* = 8.3 Hz, 1 H, CH_2O), 4.12 (dd, *J* = 8.8, 2.5 Hz, 1 H, CH_2O), 3.61 (s, 3 H, NCH_3), 3.59 (s, 3 H, NCH_3), 3.30 (dd, *J* = 13.6, 3.4 Hz, 1 H, $ArCH_2$), 2.82 (dd, *J* = 13.4, 9.8 Hz, 1 H, $ArCH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.6, 153.5, 144.2, 135.1, 134.8, 129.6, 129.5 (2 C), 129.0 (2 C), 128.9 (2 C), 127.38 (2 C), 127.36, 114.2, 67.8, 67.2, 63.9, 55.5, 51.2, 50.8, 38.0.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{27}N_2O_3$: 379.2016; found: 379.2029.

(*E*)-*N*-(2-Methoxy-2-oxoethyl)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-aminium Iodide (1a)

Methyl Cinnamylglycinate

To a solution of methyl glycinate hydrochloride (1.435 g, 11.43 mmol) in MeCN (29 mL) was added (*E*)-(3-chloroprop-1-enyl)benzene (435 mg, 2.86 mmol) and Et_3N (1.912 mL, 13.72 mmol). The mixture was stirred at reflux for 2 h. Then, the solvent was removed under reduced pressure, H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (7 × 30 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and purified by column chromatography (silica gel, 3–10% MeOH/CH_2Cl_2) to give the product (586 mg, 47%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 2 H, Ar), 7.33–7.28 (m, 2 H, Ar), 7.25–7.19 (m, 1 H, Ar), 6.54 (d, *J* = 15.9 Hz, 1 H, ArC*H*), 6.25 (dt, *J* = 15.9, 6.4 Hz, 1 H, C*H*CH_2), 3.73 (s, 3 H, OCH_3), 3.46 (s, 2 H, $COCH_2$), 3.44 (dd, *J* = 6.4, 1.3 Hz, 2 H, CHCH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 136.9, 131.9, 128.5 (2 C), 127.6, 127.5, 126.3 (2 C), 51.8, 51.3, 49.8.

Analytical data are in agreement with the literature data.[41]

(*E*)-*N*-(2-Methoxy-2-oxoethyl)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-aminium Iodide (1a)

To a solution of methyl cinnamylglycinate (1.024 g, 4.99 mmol) in MeCN (100 mL) was added K_2CO_3 (655 mg, 4.74 mmol) and MeI (2.485 mL, 39.91 mmol) under an argon atmosphere. The mixture was stirred at reflux for 2 h. After cooling to rt, K_2CO_3 was removed by filtration, the solvent was removed under reduced pressure, and the crude was purified by recrystallization (MeCN/Et_2O) to give the product (1.044 g, 90%) as fine yellow crystals; mp 162–165 °C.

^1H NMR (400 MHz, DMSO): δ = 7.60 (d, *J* = 7.1 Hz, 2 H, Ar), 7.46–7.31 (m, 3 H, Ar), 6.89 (d, *J* = 15.7 Hz, 1 H, ArC*H*), 6.50 (dt, *J* = 15.4, 7.5 Hz, 1 H, C*H*CH_2), 4.44 (s, 2 H, $COCH_2$), 4.32 (d, *J* = 7.5 Hz, 2 H, CHCH_2), 3.77 (s, 3 H, OCH_3), 3.24 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, DMSO): δ = 165.3, 141.4, 135.1, 129.1, 128.7 (2 C), 127.3 (2 C), 116.1, 66.5, 60.3, 52.9, 50.7 (2 C).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{20}NO_2$: 234.1489; found: 234.1499.

(*E*)-*N*-Benzyl-*N*-methyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]-3-phenylprop-2-en-1-aminium Bromide (1f)

(*E*)-*N*-Methyl-3-phenylprop-2-en-1-amine

To a solution of (*E*)-(3-chloroprop-1-enyl)benzene (468 mg, 3.08 mmol) in abs EtOH (3 mL) was added NaI (92 mg, 0.62 mmol) and the mixture was stirred 15 min at rt. The mixture was then cooled to 0 °C and $MeNH_2$ (2.636 mL, 30.75 mmol, 40 wt% in H_2O) was added dropwise. When the addition was complete, the mixture was allowed to warm to rt and it was stirred for 20 h. The mixture was concentrated, and the residue was taken up in CH_2Cl_2. The organic layer was washed with aq 1 M HCl , then the aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with aq 1 M HCl. The pH of the combined aqueous layers was adjusted to 12 with aq NH_4OH solution and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the product (231 mg, 51%) as a pale yellow liquid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2 H, Ar), 7.33–7.28 (m, 2 H, Ar), 7.25–7.19 (m, 1 H, Ar), 6.53 (d, *J* = 15.9 Hz, 1 H, ArC*H*), 6.29 (dt, *J* = 15.9, 6.3 Hz, 1 H, C*H*CH_2), 3.38 (dd, *J* = 6.3, 1.4 Hz, 2 H, CHCH_2), 2.48 (s, 3 H, CH_3).

Analytical data are in agreement with the literature data.[42]

3-(*N*-Cinnamyl-*N*-methylglycyl)oxazolidin-2-one

To a solution of (*E*)-*N*-methyl-3-phenylprop-2-en-1-amine (231 mg, 1.57 mmol) in MeCN (5.2 mL) was added DIPEA (410 µL, 2.35 mmol) and 3-(2-bromoacetyl)oxazolidin-2-one (326 mg, 1.57 mmol). The mixture was stirred at rt for 2 h, then the solvent was removed under reduced pressure, the residue was taken up in CH_2Cl_2 and sat. aq NH_4Cl was added. The aqueous phase was extracted with CH_2Cl_2 (10 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, and purified by column chromatography (silica gel, 5–15% EtOAc/$CHCl_3$) to give the product (319 mg, 74%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 2 H, Ar), 7.34–7.28 (m, 2 H, Ar), 7.26–7.20 (m, 1 H, Ar), 6.55 (d, *J* = 15.9 Hz, 1 H, ArC*H*), 6.31 (dt, *J* = 15.9, 6.8 Hz, 1 H, C*H*CH_2), 4.40 (t, *J* = 8.1 Hz, 2 H, CH_2O), 4.00 (t, *J* = 8.1 Hz, 2 H, CH_2N), 3.91 (s, 2 H, $COCH_2$), 3.38 (d, *J* = 6.5 Hz, 2 H, CHCH_2), 2.48 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 153.5, 136.7, 133.6, 128.6 (2 C), 127.7, 126.4 (2 C), 126.3, 62.6, 60.0, 58.8, 42.9, 42.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}NaN_2O_3$: 297.1210; found: 297.1214.

(*E*)-*N*-Benzyl-*N*-methyl-*N*-[2-oxo-2-(2-oxooxazolidin-3-yl)ethyl]-3-phenylprop-2-en-1-aminium Bromide (1f)

To a solution of 3-(*N*-cinnamyl-*N*-methylglycyl)oxazolidin-2-one (119 mg, 0.43 mmol) in MeCN (870 μL) was added BnBr (52 μL, 0.43 mmol). The mixture was stirred at rt for 24 h, then dried under reduced pressure and the residue was refluxed in EtOAc to give the product (150 mg, 78%) as fine white crystals; mp 91–94 °C.

IR (KBr): 3061, 3027, 3007, 2962, 2920, 1778, 1702, 1453, 1391, 1298, 1224, 1127, 1038, 803, 736, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.28 (m, 10 H, Ar), 6.96 (d, *J* = 15.6 Hz, 1 H, ArC*H*), 6.41 (dt, *J* = 15.4, 7.5 Hz, 1 H, C*H*CH_2), 5.35–5.19 (m, 2 H, $ArCH_2$), 5.19–5.02 (m, 2 H, $COCH_2$), 4.93–4.80 (m, 1 H, CHCH_2), 4.63–4.55 (m, 1 H, CHCH_2), 4.55–4.44 (m, 2 H, CH_2O), 4.13–4.03 (m, 2 H, CH_2N), 3.43 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 153.3, 144.0, 134.7, 133.3 (2 C), 131.0, 129.6, 129.5 (2 C), 128.9 (2 C), 127.5 (2 C), 127.1, 114.2, 66.2, 64.5, 63.5, 59.9, 48.0, 42.6.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{25}N_2O_3$: 365.1860; found: 365.1873.

Diastereomeric [2,3]-Sigmatropic Rearrangement Reaction of Ammonium Salts 1a–l; General Procedure

The solution or suspension of ammonium salt **1** (1 equiv) and TBD (1.1 equiv) was stirred in $CHCl_3$ (0.25 M solution) at rt for 1 min. The mixture was concentrated and the crude was purified by column chromatography (silica gel). Diastereomers were not separable by column chromatography. A diastereomeric ratio after the purification is shown.

Methyl 2-(Dimethylamino)-3-phenylpent-4-enoate (2a)

Following the general procedure, starting from **1a** (36 mg, 0.10 mmol). Purification by column chromatography (1–5% EtOAc/CH_2Cl_2) gave the product (15 mg, 75%) as a white solid; dr *syn*/*anti* 42:58 (^{1}H NMR).

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.07 (m, 5 H, Ar), 6.18 (ddd, *J* = 17.0, 10.1, 8.4 Hz, 1 H, CH_2CH), 5.23–5.13 (m, 2 H, CH_2CH), 3.87–3.77 (m, 1 H, COCH), 3.71–3.59 (m, 1 H, ArCH), 3.47 (s, 3 H, OCH_3), 2.45 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 140.8, 138.9, 128.55 (2 C), 128.2 (2 C), 126.9, 116.1, 71.8, 50.6, 49.8, 41.3 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.07 (m, 5 H, Ar), 5.97–5.86 (m, 1 H, CH_2CH), 5.14–5.02 (m, 2 H, CH_2CH), 3.87–3.77 (m, 1 H, COCH), 3.75 (s, 3 H, OCH_3), 3.71–3.59 (m, 1 H, ArCH), 2.30 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 140.8, 138.6, 128.54 (2 C), 127.9 (2 C), 126.7, 116.6, 70.9, 50.7, 50.1, 41.4 (2 C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_2$: 234.1489; found: 234.1478.

3-[2-(Dimethylamino)-3-phenylpent-4-enoyl]oxazolidin-2-one (2b)

Following the general procedure, starting from *trans*-**1b** (74 mg, 0.20 mmol) or *cis*-**1b** (74 mg, 0.20 mmol). Purification by column chromatography (5–15% EtOAc/CH_2Cl_2) gave the product (55 mg, 95% from *trans*-**1b**; 55 mg, 95% from *cis*-**1b**) as a white solid; dr *syn*/*anti* 92:8 (from *trans*-**1b**), 95:5 (from *cis*-**1b**) (^{1}H NMR).

IR (KBr): 2980, 2937, 2867, 2831, 2789, 1769, 1689, 1484, 1387, 1365, 1218, 1205, 1108, 1041, 932, 758, 703, 668 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 4 H, Ar), 7.21–7.15 (m, 1 H, Ar), 5.84 (ddd, *J* = 17.1, 10.1, 8.9 Hz, 1 H, CH_2CH), 5.36 (d, *J* = 11.3 Hz, 1 H, COCH), 5.02 (dt, *J* = 17.0, 1.0 Hz, 1 H, CH_2CH), 4.92 (dd, *J* = 10.1, 1.4 Hz, 1 H, CH_2CH), 4.38–4.29 (m, 2 H, CH_2O), 4.06–3.88 (m, 2 H, CH_2N), 3.79 (dd, *J* = 11.2, 8.9 Hz, 1 H, ArCH), 2.22 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 153.6, 140.9, 138.7, 128.6 (2 C), 128.1 (2 C), 126.7, 116.8, 65.2, 61.9, 50.4, 42.1, 41.2 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 4 H), 7.21–7.15 (m, 1 H), 6.12 (ddd, *J* = 16.5, 10.7, 8.6 Hz, 1 H), 5.29 (d, *J* = 11.5 Hz, 1 H), 5.12–5.09 (m, 1 H), 5.09–5.05 (m, 1 H), 4.20–4.09 (m, 1 H), 3.95–3.87 (m, 1 H), 3.77–3.71 (m, 2 H), 3.52–3.35 (m, 1 H), 2.41 (s, 6 H).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{20}NaN_2O_3$: 311.1366; found: 311.1371.

tert-Butyl [2-(Dimethylamino)-3-phenylpent-4-enoyl]carbamate (2c)

Following a modification of the general procedure, starting from **1c** (80 mg, 0.20 mmol), the mixture was stirred in the presence of TBD (56 mg, 0.40 mmol) for 30 min. Purification by column chromatography (10–15% EtOAc/CH_2Cl_2) gave the product (51 mg, 80%) as a white solid; dr 50:50 (^{1}H NMR).

IR (KBr): 3106, 3076, 2996, 2936, 2882, 2838, 2785, 1742, 1691, 1502, 1455, 1370, 1236, 1152, 1073, 987, 914, 856, 752, 697 cm^{-1}.

IR (film): 3272, 2980, 2935, 2834, 2791, 1755, 1694, 1514, 1455, 1393, 1231, 1147, 989, 917, 857, 756, 700 cm^{-1}.

Diastereomer 1 (I1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (br s, 1 H, NH), 7.37–7.13 (m, 5 H, Ar), 6.23–6.12 (m, 1 H, CH_2CH), 5.17–5.09 (m, 2 H, CH_2CH), 3.89–3.83 (m, 1 H, ArCH), 2.44 (s, 6 H, $N(CH_3)_2$), 1.41 (s, 9 H, $C(CH_3)_3$).

Diastereomer 2 (I2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (br s, 1 H, NH), 7.37–7.13 (m, 5 H, Ar), 6.08–5.95 (m, 1 H, CH_2CH), 5.13–5.00 (m, 2 H, CH_2CH), 3.85–3.78 (m, 1 H, ArCH), 2.28 (s, 6 H, $N(CH_3)_2$), 1.51 (s, 9 H, $C(CH_3)_3$).

Both Isomers

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9 (2 C) (CHCO), 150.0 (OCO), 149.8 (OCO), 141.5 (I2, *i*-Ar), 140.7 (I1, *i*-Ar), 138.9 (I2, CH_2CH), 138.5 (I1, CH_2CH), 128.5 (4 C) (*m*-Ar), 128.4 (2 C) (*o*-Ar), 128.2 (2 C) (*o*-Ar),

126.8 (*p*-Ar), 126.6 (*p*-Ar), 116.8 (I1, *C*H$_2$CH), 116.2 (I2, *C*H$_2$CH), 82.5 (I2, *C*(CH$_3$)$_3$), 82.3 (I1, *C*(CH$_3$)$_3$), 69.9 (*C*HCO), 68.8 (*C*HCO), 49.9 (I2, ArCH), 49.8 (I1, ArCH), 41.9 (2 C) (I1, N(CH$_3$)$_2$), 41.4 (2 C) (I2, N(CH$_3$)$_2$), 28.0 (3 C) (I2, C(*C*H$_3$)$_3$), 27.9 (3 C) (I1, C(*C*H$_3$)$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}N_2O_3$: 319.2016; found: 319.2024.

3-[3-Phenyl-2-(pyrrolidin-1-yl)pent-4-enoyl]oxazolidin-2-one (2e)

Following the general procedure, starting from **1e** (37 mg, 0.09 mmol). Purification by column chromatography (20–25% EtOAc/CH$_2$Cl$_2$) gave the product (25 mg, 86%) as a white solid; dr *syn*/*anti* 90:10 (^{1}H NMR).

IR (KBr): 3027, 2966, 2831, 2801, 1774, 1693, 1385, 1360, 1216, 1201, 1105, 1040, 759, 702 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29–7.12 (m, 5 H, Ar), 6.01–5.91 (m, 1 H, CH$_2$C*H*), 5.46 (d, *J* = 10.5 Hz, 1 H, COCH), 5.08–5.01 (m, 1 H, C*H*$_2$CH), 4.96 (dd, *J* = 10.2, 1.3 Hz, 1 H, C*H*$_2$CH), 4.35–4.27 (m, 1 H, CH$_2$O), 4.28–4.22 (m, 1 H, CH$_2$O), 4.01–3.94 (m, 1 H, CH$_2$N), 3.90–3.81 (m, 2 H, ArCH, CH$_2$N), 2.72–2.63 (m, 2 H, NCH$_2$), 2.58–2.49 (m, 2 H, NCH$_2$), 1.53–1.44 (m, 4 H, (CH$_2$)$_2$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 172.3, 153.5, 141.2, 138.5, 128.4 (2 C), 128.1 (2 C), 126.5, 116.7, 63.2, 61.9, 51.5, 48.9 (2 C), 42.2, 23.5 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29–7.11 (m, 5 H), 6.17 (ddd, *J* = 16.9, 10.4, 8.2 Hz, 1 H), 5.51 (d, *J* = 11.4 Hz, 1 H), 5.06–4.99 (m, 2 H), 4.19–4.09 (m, 1 H), 4.01–3.92 (m, 1 H), 3.90–3.81 (m, 1 H), 3.79–3.71 (m, 1 H), 3.46–3.36 (m, 1 H), 2.97–2.84 (m, 2 H), 2.75–2.63 (m, 2 H), 1.74–1.62 (m, 4 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_3$: 315.1703; found: 315.1713.

3-{2-[Benzyl(methyl)amino]-3-phenylpent-4-enoyl}oxazolidin-2-one (2f)

Following the general procedure, starting from **1f** (42 mg, 0.09 mmol). Purification by column chromatography (1–2% EtOAc/CH$_2$Cl$_2$) gave the product (25 mg, 74%) as a colorless oil; dr (*syn*/*anti*) 85:15 (^{1}H NMR).

IR (KBr): 3062, 3027, 2982, 2924, 2799, 1775, 1693, 1453, 1385, 1217, 1104, 1041, 759, 701 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.36–7.15 (m, 5 H, Ar), 7.07–6.98 (m, 3 H, Ar), 6.71–6.61 (m, 2 H, Ar), 5.87 (ddd, *J* = 17.1, 9.9, 8.9 Hz, 1 H, CH$_2$C*H*), 5.50 (d, *J* = 11.4 Hz, 1 H, COCH), 5.07–5.00 (m, 1 H, C*H*$_2$CH), 4.95–4.89 (dd, *J* = 10.3, 1.1 Hz, 1 H, C*H*$_2$CH), 4.40–4.28 (m, 2 H, CH$_2$O), 4.04–3.91 (m, 2 H, CH$_2$N), 3.91–3.82 (m, 1 H, ArCH), 3.75 (d, *J* = 13.8 Hz, 1 H, ArCH$_2$), 3.36 (d, *J* = 13.8 Hz, 1 H, ArCH$_2$), 2.08 (s, 3 H, CH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 172.3, 153.6, 140.7, 139.5, 138.6, 128.6 (2 C), 128.4 (2 C), 128.2 (2 C), 127.9 (2 C), 126.6 (2 C), 116.8, 65.3, 61.9, 57.4, 50.9, 42.1, 37.8.

Minor Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34–7.08 (m, 10 H), 6.23 (ddd, *J* = 18.1, 10.1, 8.3 Hz, 1 H), 5.44 (d, *J* = 11.5 Hz, 1 H), 5.16–5.06 (m, 2 H), 4.17–4.08 (m, 1 H), 4.05–3.92 (m, 1 H), 3.97–3.90 (m, 1 H), 3.93–3.85 (m, 1 H), 3.80–3.69 (m, 1 H), 3.60 (d, *J* = 13.6 Hz, 1 H), 3.50–3.40 (m, 1 H), 2.25 (s, 3 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}N_2O_3$: 365.1860; found: 365.1867.

3-[2-(Dimethylamino)-3-methylpent-4-enoyl]oxazolidin-2-one (2g)

Following a modification of the general procedure, starting from *trans*-**1g** (127 mg, 0.41 mmol) or *cis*-**1g** (118 mg, 0.38 mmol), the reaction was stirred in freshly distilled CHCl$_3$ (1.6 mL and 1.5 mL, respectively) under an argon atmosphere in the presence of powdered 4 Å molecular sieves (300 mg and 220 mg, respectively). Purification by column chromatography (5–15% EtOAc/CH$_2$Cl$_2$) gave the product (57 mg, 61% from *trans*-**1g**; 45 mg, 52% from *cis*-**1g**) as a pale yellow amorphous solid; dr *syn*/*anti* 60:40 (*trans*-**1g**), 58:42 (*cis*-**1g**) (^{1}H NMR).

IR (KBr): 2979, 2934, 2871, 2831, 2791, 1776, 1692, 1454, 1385, 1361, 1218, 1204, 1104, 1040, 920, 761 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.66 (ddd, *J* = 17.2, 10.1, 8.7 Hz, 1 H, CH$_2$C*H*), 5.01 (dd, *J* = 17.1, 2.7 Hz, 1 H, C*H*$_2$CH), 4.93 (dd, *J* = 10.2, 1.8 Hz, 1 H, C*H*$_2$CH), 4.66 (d, *J* = 10.8 Hz, 1 H, COCH), 4.37 (dd, *J* = 8.8, 7.3 Hz, 2 H, CH$_2$O), 4.12–3.98 (m, 2 H, CH$_2$N), 2.71–2.57 (m, 1 H, CH$_3$C*H*), 2.36 (s, 6 H, N(CH$_3$)$_2$), 1.10 (d, *J* = 6.7 Hz, 3 H, CH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 172.2, 153.5, 140.4, 116.0, 66.3, 61.8, 42.0, 41.1 (2 C), 38.6, 17.2.

Minor Diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.85 (ddd, *J* = 17.3, 10.2, 8.5 Hz, 1 H, CH$_2$C*H*), 5.15–5.09 (m, 1 H, C*H*$_2$CH), 5.07 (dd, *J* = 10.2, 1.8 Hz, 1 H, C*H*$_2$CH), 4.72 (d, *J* = 10.7 Hz, 1 H, COCH), 4.46–4.38 (m, 2 H, CH$_2$O), 4.01–3.87 (m, 2 H, CH$_2$N), 2.85–2.70 (m, 1 H, CH$_3$C*H*), 2.35 (s, 6 H, N(CH$_3$)$_2$), 0.94 (d, *J* = 6.7 Hz, 3 H, CH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 171.5, 153.4, 141.1, 114.7, 66.6, 61.84, 42.2, 41.1 (2 C), 37.6, 17.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}N_2O_3$: 227.1390; found: 227.1393.

3-[2-(Dimethylamino)pent-4-enoyl]oxazolidin-2-one (2h)

Following a modification of the general procedure, starting from **1h** (118 mg, 0.40 mmol), the mixture was stirred in freshly distilled CHCl$_3$ (1.6 mL) under an argon atmosphere in the presence of powdered 4 Å molecular sieves (300 mg). Purification by column chromatography (50–55% EtOAc/CH$_2$Cl$_2$) gave the product (68 mg, 80%) as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.83–5.68 (m, 1 H, CH$_2$C*H*), 5.09 (dd, *J* = 17.0, 1.5 Hz, 1 H, C*H*$_2$CH), 5.02 (dd, *J* = 10.2, 1.4 Hz, 1 H, C*H*$_2$CH), 4.72 (dd, *J* = 8.9, 5.7 Hz, 1 H, COCH), 4.42–4.34 (m, 2 H, CH$_2$O), 4.05–3.95 (m, 2 H, CH$_2$N), 2.59–2.48 (m, 1 H, COCHC*H*$_2$), 2.42–2.32 (m, 1 H, COCHC*H*$_2$), 2.36 (s, 6 H, N(CH$_3$)$_2$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 172.1, 153.2, 134.4, 117.6, 62.7, 61.9, 42.4, 41.4 (2 C), 30.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}N_2O_3$: 213.1234; found: 213.1236.

3-[2-(Dimethylamino)-3-(4-methoxyphenyl)pent-4-enoyl]oxazolidin-2-one (2i)

Following the general procedure, starting from **1i** (80 mg, 0.20 mmol), Purification by column chromatography (10% EtOAc/CH_2Cl_2) gave the product (43 mg, 68%) as a white solid; dr (*syn*/*anti*) 86:14 (^{1}H NMR).

IR (KBr): 3079, 2982, 2937, 2833, 2786, 1770, 1691, 1514, 1478, 1395, 1370, 1243, 1224, 1205, 1105, 1044, 1029, 917, 812, 656 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H, Ar), 6.92–6.83 (m, 2 H, Ar), 5.87 (ddd, *J* = 17.1, 10.1, 8.8 Hz, 1 H, CH_2CH), 5.36 (d, *J* = 11.3 Hz, 1 H, COCH), 5.07–5.01 (m, 1 H, CH_2CH), 4.95 (dd, *J* = 10.1, 1.5 Hz, 1 H, CH_2CH), 4.45–4.35 (m, 2 H, CH_2O), 4.11–3.94 (m, 2 H, CH_2N), 3.79 (s, 3 H, OCH_3), 3.83–3.77 (m, 1 H, ArCH), 2.28 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9, 158.3, 153.7, 139.0, 132.9, 129.0 (2 C), 116.4, 114.1 (2 C), 65.3, 61.9, 55.2, 49.5, 42.1, 41.2 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.11 (m, 2 H), 6.83–6.76 (m, 2 H), 6.21–6.09 (m, 1 H), 5.30 (d, *J* = 11.5 Hz, 1 H), 5.14–5.07 (m, 2 H), 4.26–4.17 (m, 1 H), 4.11–3.94 (m, 1 H), 3.93–3.85 (m, 1 H), 3.83–3.76 (m, 1 H), 3.76 (s, 3 H), 3.59–3.50 (m, 1 H), 2.45 (s, 6 H, $N(CH_3)_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_4$: 319.1652; found: 319.1656.

3-[2-(Dimethylamino)-3-(4-nitrophenyl)pent-4-enoyl]oxazolidin-2-one (2j)

Following the general procedure, starting from **1j** (83 mg, 0.20 mmol). Purification by column chromatography (2–5% EtOAc/CH_2Cl_2) gave the product (60 mg, 90%) as a yellow amorphous solid; dr (*syn*/*anti*) 83:17 (^{1}H NMR).

IR (KBr): 3080, 2984, 2933, 2838, 2794, 1783, 1769, 1690, 1523, 1387, 1344, 1197, 1105, 1038, 920, 802, 729 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.15 (m, 2 H, Ar), 7.49–7.43 (m, 2 H, Ar), 5.82 (ddd, *J* = 17.0, 10.1, 8.8 Hz, 1 H, CH_2CH), 5.46 (d, *J* = 11.5 Hz, 1 H, COCH), 5.16–5.09 (m, 1 H, CH_2CH), 5.04 (dd, *J* = 10.1, 1.6 Hz, 1 H, CH_2CH), 4.49–4.39 (m, 2 H, CH_2O), 4.13–3.93 (m, 3 H, CH_2N, ArCH), 2.25 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 153.7, 148.8, 146.8, 137.0, 129.0 (2 C), 123.9 (2 C), 118.4, 64.9, 62.0, 50.3, 42.1, 41.0 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.10 (m, 2 H), 7.43–7.40 (m, 2 H), 6.19–6.08 (m, 1 H), 5.40 (d, *J* = 11.5 Hz, 1 H), 5.21–5.16 (m, 1 H), 5.13–5.07 (m, 1 H), 4.33–4.24 (m, 1 H), 4.24–4.17 (m, 1 H), 4.13–3.93 (m, 1 H), 3.92–3.86 (m, 1 H), 3.70–3.59 (m, 1 H), 2.44 (s, 6 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_5$: 334.1397; found: 334.1411.

3-[2-(Dimethylamino)-3-(naphthalen-2-yl)pent-4-enoyl]oxazolidin-2-one (2k)

Following the general procedure, starting from **1k** (84 mg, 0.20 mmol). Purification by column chromatography (10% EtOAc/CH_2Cl_2) gave the product (59 mg, 87%) as a white solid; dr (*syn*/*anti*) 87:13 (^{1}H NMR).

IR (KBr): 3004, 2972, 2931, 2832, 2785, 1778, 1684, 1388, 1358, 1202, 1120, 1043, 918, 823, 749 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.64 (m, 4 H, Ar), 7.51–7.34 (m, 3 H, Ar), 5.98 (ddd, *J* = 17.1, 10.1, 8.8 Hz, 1 H, CH_2CH), 5.55 (d, *J* = 11.3 Hz, 1 H, COCH), 5.15–5.09 (m, 1 H, CH_2CH), 5.00 (dd, *J* = 10.2, 1.4 Hz, 1 H, CH_2CH), 4.47–4.35 (m, 2 H, CH_2O), 4.14–3.97 (m, 2 H, CH_2N), 4.08–3.97 (m, 1 H, ArCH), 2.29 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.6, 151.6, 136.4, 136.3, 131.6, 130.5, 126.2, 125.6 (2 C), 124.8, 124.0, 123.8, 123.4, 114.9, 63.0, 59.8, 48.5, 40.0, 39.1 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.64 (m, 4 H), 7.51–7.34 (m, 3 H), 6.31–6.21 (m, 1 H), 5.48 (d, *J* = 11.5 Hz, 1 H), 5.19–5.15 (m, 2 H), 4.14–4.07 (m, 1 H), 3.76–3.70 (m, 2 H), 3.43–3.36 (m, 2 H), 2.50 (s, 6 H, $N(CH_3)_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_3$: 339.1703; found: 339.1708.

3-[2-(Dimethylamino)-3-(thiophen-2-yl)pent-4-enoyl]oxazolidin-2-one (2l)

Following the general procedure, starting from **1l** (75 mg, 0.20 mmol). Purification by column chromatography (5–7% EtOAc/CH_2Cl_2) gave the product (49 mg, 83%) as a white solid; dr (*syn*/*anti*) 85:15 (^{1}H NMR).

IR (KBr): 2977, 2937, 2876, 2803, 1770, 1682, 1454, 1394, 1369, 1223, 1110, 1045, 922, 712 cm^{-1}.

Major Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.18 (m, 1 H, Ar), 6.98–6.93 (m, 2 H, Ar), 5.90 (ddd, *J* = 17.1, 10.1, 8.9 Hz, 1 H, CH_2CH), 5.22 (d, *J* = 11.2 Hz, 1 H, COCH), 5.19–5.12 (m, 1 H, CH_2CH), 5.09 (dd, *J* = 10.1, 1.3 Hz, 1 H, CH_2CH), 4.45–4.35 (m, 2 H, CH_2O), 4.12 (dd, *J* = 11.1, 8.9 Hz, 1 H, ArCH), 4.09–3.94 (m, 2 H, CH_2N), 2.35 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 153.5, 143.8, 137.7, 126.3, 125.0, 124.6, 118.0, 66.0, 61.9, 44.8, 42.1, 41.1 (2 C).

Minor Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.11 (m, 1 H), 6.91–6.87 (m, 2 H), 6.10 (ddd, *J* = 16.9, 10.2, 8.5 Hz, 1 H), 5.30 (d, *J* = 11.4 Hz, 1 H), 5.20–5.14 (m, 2 H), 4.33–4.25 (m, 1 H), 4.23–4.15 (m, 2 H), 3.96–3.88 (m, 1 H), 3.77–3.69 (m, 1 H), 2.44 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 153.2, 143.5, 138.7, 126.9, 124.7, 124.1, 116.0, 66.2, 61.8, 44.6, 42.2, 41.0 (2 C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_3S$: 295.1111; found: 295.1115.

(4*S*)-4-Benzyl-3-[2-(dimethylamino)-3-phenylpent-4-enoyl]-oxazolidin-2-one (2m)

Following the general procedure, starting from **1m** (200 mg, 0.44 mmol). Purification by column chromatography (5–10% EtOAc/CH_2Cl_2) gave the product (140 mg, 85%) as a white solid; dr (*syn*/*anti*) 84:8:7:1.

IR (KBr): 3027, 2978, 2937, 2867, 2834, 2793, 1769, 1688, 1390, 1365, 1197, 1106, 922, 758, 703 cm^{-1}.

Major Diastereomer

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 10 H, Ar), 5.85 (ddd, *J* = 17.1, 10.0, 8.9 Hz, 1 H, CH_2CH), 5.37 (d, *J* = 11.3 Hz, 1 H, COCH), 5.07–5.01 (m, 1 H, CH_2CH), 4.93 (dd, *J* = 10.2, 1.4 Hz, 1 H, CH_2CH), 4.66 (ddt, *J* = 10.7, 7.4, 3.8 Hz, 1 H, NCH), 4.12–4.02 (m, 2 H, OCH_2), 3.82 (dd, *J* = 11.2, 8.8 Hz, 1 H, ArCH), 3.36 (dd, *J* = 13.3, 3.5 Hz, 1 H, $ArCH_2$), 2.64 (dd, *J* = 13.3, 10.2 Hz, 1 H, $ArCH_2$), 2.29 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 153.7, 140.9, 138.7, 135.4, 129.4 (2 C), 129.0 (2 C), 128.6 (2 C), 128.1 (2 C), 127.4, 126.7, 116.9, 66.1, 65.4, 55.3, 50.4, 41.2 (2 C), 39.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_3$: 379.2016; found: 379.2024.

3-[2-(Dimethylamino)-3-phenylpent-4-enoyl]oxazolidin-2-one (2b); 1-mmol Scale Reaction

Following the general procedure, starting from *trans*-**1b** (369 mg, 1.00 mmol). Purification by column chromatography (10% EtOAc/CH_2Cl_2) gave the product (270 mg, 94%) as a white solid; dr (*syn*/*anti*) 93:7 (^1H NMR).

Epimerization Assay

To a solution of compound **2a**, **2b**, **2i**, or **2k** (the dr of the isolated compounds) (1 equiv) in $CDCl_3$ (0.25 M solution) was added TBD (1 equiv). The mixture was stirred at rt for 24 h. The dr of **2a**, **2b**, **2i** or **2k** was determined by ^1H NMR and it did not change during the reaction.

2-(Dimethylamino)-*N*-(2-hydroxyethyl)-3-phenylpent-4-enamide (3) from 2b

To a solution of **2b** (190 mg, 0.66 mmol) in MeOH (1.3 mL) was added NaOMe (43 mg, 0.79 mmol). The mixture was stirred at rt for 5 min, after this time TLC showed full consumption of the starting compound. The mixture was dried under reduced pressure and the obtained residue was purified by column chromatography (7–10% MeOH/CH_2Cl_2) to give the product (172 mg, 99%) as a white solid; dr (*syn*/*anti*) 90:10 (^1H NMR).

IR (KBr): 3300, 3033, 2935, 2875, 2830, 2785, 1645, 1544, 1452, 1267, 1216, 1063, 915, 757, 700 cm^{-1}.

Major Diastereomer

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 2 H, Ar), 7.28–7.19 (m, 3 H, Ar), 6.41 (br s, 1 H, NH), 6.17–6.07 (m, 1 H, CH_2CH), 5.11–5.07 (m, 1 H, CH_2CH), 5.08–5.02 (m, 1 H, CH_2CH), 3.82 (t, *J* = 8.4 Hz, 1 H, ArCH), 3.71–3.61 (m, 2 H, CH_2OH), 3.44–3.35 (m, 2 H, $NHCH_2$), 3.18 (d, *J* = 8.2 Hz, 1 H, COCH), 2.29 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 141.7, 138.4, 128.5 (2 C), 128.2 (2 C), 126.6, 116.7, 73.8, 62.5, 50.1, 42.6 (2 C), 42.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_2$: 263.1754; found: 263.1746.

2-Aminoethyl 2-(Dimethylamino)-3-phenylpent-4-enoate (4) from 3

To a solution of **3** (400 mg, 1.52 mmol) in dioxane (9 mL) was added aq 5 M H_2SO_4 (9.148 mL, 45.74 mmol). The mixture was stirred at 100 °C for 16 h. The mixture was cooled and the pH of the solution was regulated to 7 with sat. aq $NaHCO_3$ solution. The organic phase was extracted promptly with CH_2Cl_2 (7 ×) and dried (Na_2SO_4). After filtration, the residue was purified by column chromatography (silica gel, 1–3% MeOH/NH_3 in CH_2Cl_2) to give the product (281 mg, 70%) as an orange oil; dr (*syn*/*anti*) 89:11 (^1H NMR).

IR (KBr): 3293, 3028, 2935, 2869, 2838, 2788, 1730, 1649, 1557, 1453, 1257, 1213, 1162, 921, 757, 700 cm^{-1}.

Major Diastereomer

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H, Ar), 7.23–7.19 (m, 3 H, Ar), 5.89 (ddd, *J* = 17.1, 10.2, 8.4 Hz, 1 H, CH_2CH), 5.08 (dt, *J* = 17.0, 1.3 Hz, 1 H, CH_2CH), 5.02 (dd, *J* = 10.2, 2.0 Hz, 1 H, CH_2CH), 4.21–4.07 (m, 2 H, NH_2CH_2), 3.76 (dd, *J* = 11.2, 8.5 Hz, 1 H, ArCH), 3.61 (d, *J* = 11.2 Hz, 1 H, COCH), 2.92 (t, *J* = 5.5 Hz, 2 H, OCH_2), 2.26 (s, 6 H, $N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 140.7, 138.6, 128.6, 127.9, 126.7, 116.7, 71.0, 66.4, 50.1, 41.4, 41.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_2$: 263.1754; found: 263.1758.

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Supporting Information

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References

(1) Present address: S. Kaabel, Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada.
(2) For a recent review, see: (a) Wolfe, J. P. In *Comprehensive Organic Synthesis, 2nd ed., Vol. 3*; Knochel, P.; Molander, G. A., Ed.; Elsevier: Amsterdam, **2014**, 1038. (b) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446.
(3) Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. *Org. Lett.* **2016**, *18*, 1358.
(4) Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. *J. Org. Chem.* **2017**, *82*, 2889.
(5) Drouillat, B.; Wright, K.; Quinodoz, P.; Marrot, J.; Couty, F. *J. Org. Chem.* **2015**, *80*, 6936.

(6) (a) Åhman, J.; Somfai, P. *J. Am. Chem. Soc.* **1994**, *116*, 9781. (b) Åhman, J.; Jarevång, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148.
(7) (a) Anderson, J. C.; Siddons, D. G.; Smith, S. C.; Swarbrick, M. E. *J. Org. Chem.* **1996**, *61*, 4820. (b) Anderson, J. C.; Smith, S. C.; Swarbrick, M. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1517. (c) Anderson, J. C.; Flaherty, A.; Swarbrick, M. E. *J. Org. Chem.* **2000**, *65*, 9152. (d) Anderson, J. C.; Davies, E. A. *Tetrahedron* **2010**, *66*, 6300.
(8) Murata, Y.; Nakai, T. *Chem. Lett.* **1990**, 2069.
(9) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2817.
(10) (a) Blid, J.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 3159. (b) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043.
(11) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193.
(12) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027. (b) Tayama, E. *Heterocycles* **2016**, *92*, 793.
(13) (a) Biswas, B.; Collins, S. C.; Singleton, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 3740. (b) Biswas, B.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 14244. (c) Tayama, E. *Chem. Rec.* **2015**, *15*, 789. (d) Tayama, E.; Kimura, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 8869.
(14) Jemison, R. W.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1969**, 294.
(15) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 12956.
(16) Zhang, J.; Chen, Z.-X.; Du, T.; Li, B.; Gu, Y.; Tian, S.-K. *Org. Lett.* **2016**, *18*, 4872.
(17) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, 1077.
(18) Tayama, E.; Naganuma, N.; Iwamoto, H.; Hasegawa, E. *Chem. Commun.* **2014**, *50*, 6860.
(19) Anderson, J. C.; Ford, J. G.; Whiting, M. *Org. Biomol. Chem.* **2005**, *3*, 3734.
(20) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31.
(21) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352.
(22) (a) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066. (b) Sweeney, J. B.; Tavassoli, A.; Workman, J. A. *Tetrahedron* **2006**, *62*, 11506.
(23) (a) West, T. H.; Daniels, D. S.; Slawin, A. M.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476. (b) West, T. H.; Walden, D. M.; Taylor, J. E.; Brueckner, A. C.; Johnston, R. C.; Cheong, P. H.-Y.; Lloyd-Jones, G. C.; Smith, A. D. *J. Am. Chem. Soc.* **2017**, *139*, 4366. (c) West, T. H.; Spoehrle, S. S. M.; Smith, A. D. *Tetrahedron* **2017**, *73*, 4138.
(24) For selected references, see: (a) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1973**, 656. (b) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1953. (c) Hayes, J. F.; Tavassoli, A.; Sweeney, J. B. *Synlett* **2000**, 1208.
(25) Markó, I. E. In *Comprehensive Organic Synthesis, Vol. 3*; Trost, B. M.; Fleming, I., Ed.; Pergamon: Oxford, **1991**, 913.
(26) Davies, S. G.; Hunter, I. A.; Nicholson, R. L.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2004**, *60*, 7553.
(27) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.
(28) Prashad, M.; Shieh, W.-C.; Liu, Y. *Tetrahedron* **2016**, *72*, 17.
(29) Stevens, J. M.; Parra-Rivera, A. C.; Dixon, D. D.; Beutner, G. L.; DelMonte, A. J.; Frantz, D. E.; Janey, J. M.; Paulson, J.; Talley, M. R. *J. Org. Chem.* **2018**, *83*, 14245.
(30) Guissart, C.; Barros, A.; Barata, L. R.; Evano, G. *Org. Lett.* **2018**, *20*, 5098.
(31) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268.
(32) Kanomata, N.; Maruyama, S.; Tomono, K.; Anada, S. *Tetrahedron Lett.* **2003**, *44*, 3599.
(33) Devaraj, N. K.; Perrin, C. L. *Chem. Sci.* **2018**, *9*, 1789.
(34) Hirata, G.; Satomura, H.; Kumagae, H.; Shimizu, A.; Onodera, G.; Kimura, M. *Org. Lett.* **2017**, *19*, 6148.
(35) Antonsson, T.; Moberg, C. *Organometallics* **1985**, *4*, 1083.
(36) Sirlin, C.; Chengebroyen, J.; Konrath, R.; Ebeling, G.; Raad, I.; Dupont, J.; Paschaki, M.; Kotzyba-Hibert, F.; Harf-Monteil, C.; Pfeffer, M. *Eur. J. Org. Chem.* **2004**, 1724.
(37) Valenta, V.; Vlková, M.; Valchář, M.; Dobrovský, K.; Polívka, Z. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1525.
(38) Dias, L. C.; Melgar, G. Z.; Jardim, L. S. A. *Tetrahedron Lett.* **2005**, *46*, 4427.
(39) Agasimundin, Y. S.; Oakes, F. T.; Leonard, N. J. *J. Org. Chem.* **1985**, *50*, 2474.
(40) Lücke, D.; Linne, Y.; Hempel, K.; Kalesse, M. *Org. Lett.* **2018**, *20*, 4475.
(41) Taaning, R. H.; Thim, L.; Karaffa, J.; Campaña, A. G.; Hansen, A.-M.; Skrydstrup, T. *Tetrahedron* **2008**, *64*, 11884.
(42) Gerpe, A.; Boiani, L.; Hernández, P.; Sortino, M.; Zacchino, S.; González, M.; Cerecetto, H. *Eur. J. Med. Chem.* **2010**, *45*, 2154.

Appendix 2

Publication II

Murre, A.; Erkman, K.; Järving, I.; Kanger, T. Asymmetric Chemoenzymatic One-Pot Synthesis of α-Hydroxy Half-Esters. ACS Omega **2021**, *6*, 20686–20698.

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Article

Asymmetric Chemoenzymatic One-Pot Synthesis of α-Hydroxy Half-Esters

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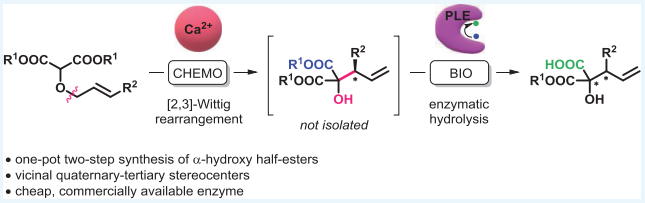

ABSTRACT: A new chemoenzymatic one-pot strategy has been developed for the synthesis of α-hydroxy half-esters containing consecutive quaternary and tertiary stereocenters using asymmetric cascade catalysis. In this study, an asymmetric Ca^{2+}-catalyzed [2,3]-Wittig rearrangement reaction was proven to be suitable for a combination with porcine liver esterase-mediated hydrolysis resulting in the enhanced enantiomeric purity of the obtained products in a one-pot synthesis compared to the stepwise method.

INTRODUCTION

An α-hydroxy-β-dicarbonyl moiety is a ubiquitous fragment in naturally occurring biomolecules and their precursors.[1] These densely functionalized motifs, including α-hydroxy half-esters are synthetically pliable building blocks and, therefore, are widely used as intermediates in numerous synthetic routes for the preparation of different pharmaceuticals.[2]

Despite the fact that stereoselective chemical transformations of α-hydroxy-β-dicarbonyl compounds have been intensively studied, most of the methods have been developed for preparation of α-hydroxy-β-ketoesters.[3] There have been only limited studies on the asymmetric synthesis of α-hydroxy half-esters, especially of α-hydroxy malonate derivatives. Both metal-catalyzed[4,5] and organocatalytic[6−8] methods have been exploited. The described methods show a synthetic path to obtain α-hydroxy diesters, which can be readily transformed to α-hydroxy half-esters by basic hydrolysis. On the other hand, biotransformations provide a wide range of opportunities to catalyze the desymmetrization of prochiral mono- and disubstituted diesters utilizing both transesterification reactions and hydrolysis. The most suitable and commonly used class of enzymes for these transformations are hydrolases. Broad substrate specificity and high stereoselectivity, in addition to the fact that hydrolases are mostly commercially available and do not require additional cofactors, have made hydrolases widely used catalysts in asymmetric synthesis.[9] Despite all of these tremendous advantages of hydrolases, the literature currently lacks proper coverage of synthetic pathways for obtaining α-hydroxy half-esters enantioselectively utilizing enzymes. Among the few reported methods, α-hydroxy half-esters were prepared enantioselectively with methodologies proposed by the Tamm[10] and Kikelj[11] groups. All of the described examples provide attractive methods to synthesize α-hydroxy half-esters, although containing only one stereogenic center.

One-pot reactions have been demonstrated to be environmentally sustainable and economically viable techniques as no isolation of the intermediate is required, which leads to increased efficiency due to the reduction of energy and time consumption and the production of waste.[12] Combinations of asymmetric organocatalytic or metal-catalytic reactions with biotransformation in a chemoenzymatic one-pot process offer a great potential to achieve this goal. However, the possible incompatibility of the different reagents or solvents used to catalyze one of the steps and the corresponding reaction conditions with an enzyme make chemoenzymatic one-pot reactions challenging.[13,14]

To the best of our knowledge, a systematic study of the creation of multiple stereogenic centers containing α-hydroxy half-esters has not been reported in the literature. In our ongoing endeavor to achieve this goal, herein, we report the asymmetric chemoenzymatic one-pot strategy for the formation of α-hydroxy half-esters bearing vicinal quaternary and tertiary stereocenters. We combine our previous study of the

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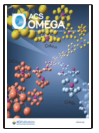

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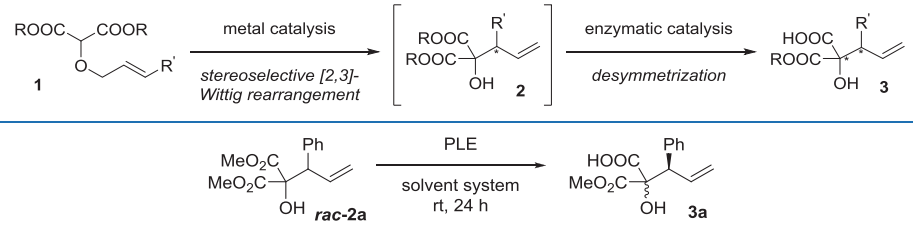
Scheme 1. Chemoenzymatic Approach to Half-Esters 3



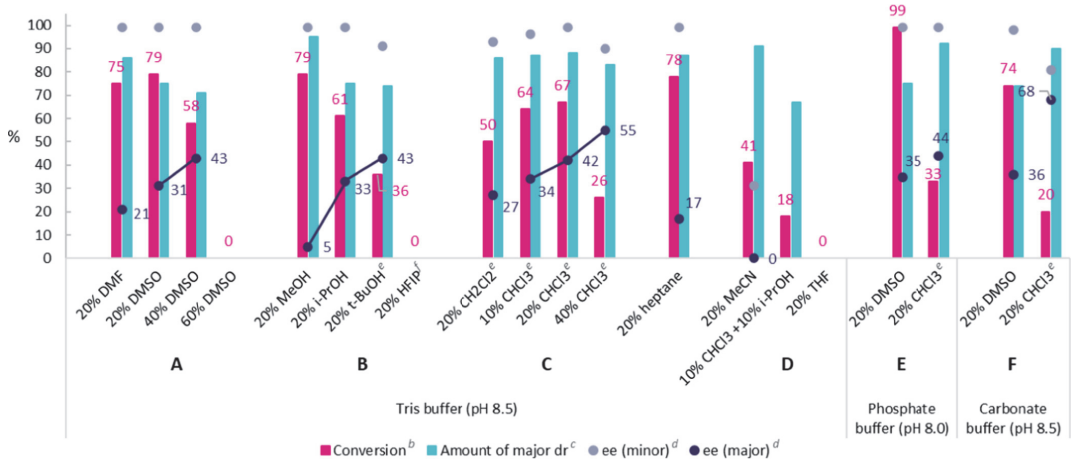


Figure 1. (A–F) Effect of co-solvents on the PLE-mediated hydrolysis of ***rac*-2a**.[a] ([a]Reaction conditions: 0.1 mmol scale, 85 EU of crude PLE, solvent system (0.2 M). [b]Conversion was determined by ^{1}H NMR analysis of the crude mixture and referred to the ratio of starting material and product. [c]Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. [d]Enantiomeric excess was determined by chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC). [e]Reaction was completed after 72 h. [f]HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol).

metal-catalyzed asymmetric [2,3]-Wittig rearrangement of allyloxy malonates **1**[15] with the following enzymatic desymmetrization of sterically demanding α-substituted diesters **2** (Scheme 1). The Wittig rearrangement affords α-hydroxy malonic derivative **2** with a single tertiary stereogenic center. In the second step of the sequence, a quaternary stereogenic center is formed affording product **3** with two contiguous highly crowded stereocenters.

■ RESULTS AND DISCUSSION

In our initial study, we set the benchmarks for the asymmetric [2,3]-Wittig rearrangement reaction and enzymatic hydrolysis separately. As the asymmetric [2,3]-Wittig rearrangement reaction was based on our previous experience, we first investigated the enzymatic hydrolysis of the racemic [2,3]-Wittig rearrangement reaction product ***rac*-2a** (Figure 1). Of a number of widely used hydrolase family enzymes,[16] we tested immobilized lipase B from *Candida antarctica* (CALB), esterase from porcine liver (PLE), lipase from porcine liver (PLL), lipase from *Candida rugosa* (CRL), and lipase from *Rhizomucor miehei* (RML). For the enantioselective desymmetrization of the racemic rearrangement product **2a**, only PLE showed catalytic activity (the conversion of the starting material under unoptimized conditions in phosphate buffer was 34%) and it was used in all further experiments (see Table S1, Supporting Information (SI)). From the screening of the most commonly used buffers at different pH values, phosphate buffer (pH 8.0, 0.2 M), Tris buffer (pH 8.5, 0.2 M), and carbonate buffer (pH 8.5, 0.2 M) were selected as starting points for the optimization of the reaction conditions. Of them, Tris buffer showed a greater diastereoisomeric ratio (dr, 1:8) with comparably high conversion (91%), and therefore it was chosen as the primary buffer (see Table S2, SI). Additionally, the influence of organic co-solvents on the rate and the selectivity of the hydrolysis step was evaluated (Figure 1). In PLE-catalyzed hydrolysis, in general, the presence of the co-solvent inhibited the enzyme activity but the stereoselectivity was very dependent on the co-solvent used. The enantioselectivity of the minor diastereoisomer was high (>90%) in almost all cases, but the enantiomeric excess (ee) of the major diastereoisomer was influenced more. The addition of 20% of dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) gave a similar conversion, but the latter showed slightly higher enantioselectivity for the major diastereoisomer (ee 31%) (Figure 1A). The enantiomeric purity of the major diastereoisomer was increased using 40% of DMSO (ee 41%), although it decreased the reaction rate significantly. Upon further increasing the DMSO percentage to 60%, no

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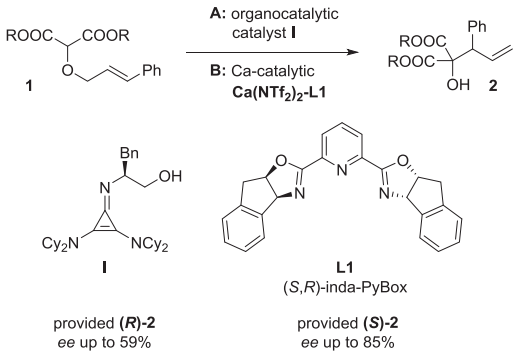
reaction was observed. When alcohols were employed, there was a strong correlation between the reaction rate, selectivity, and the bulkiness of the alcohol used (Figure 1B). The reaction in MeOH proceeded with higher conversion, diastereoselectivity, and enantioselectivity of the minor diastereoisomer than the reaction in *t*-BuOH, although the enantioselectivity of the major diastereoisomer decreased significantly (ee 5%). Surprisingly, chlorinated solvents were found to be compatible with the biotransformation, although they led to longer reaction times (Figure 1C). Also, as in the case of DMSO, a larger amount of $CHCl_3$ caused a decrease in the rate of reaction, while it increased the ee of the major diastereoisomer (ee 55%). In combination with Tris buffer at pH 8.4, 20% of heptane was able to enhance the enzyme activity resulting in 78% of conversion in 2 h, but, unfortunately, the ee of the major diastereoisomer was only 17%. Other co-solvents or combinations of them (shown in Figure 1D) either showed a detrimental effect on the enantioselectivity of the hydrolysis or did not have a reaction at all.

Our preliminary results demonstrated that enzymatic reactions using an 8:2 ratio of Tris buffer/co-solvent (DMSO or $CHCl_3$) showed an optimal conversion-to-ee ratio. Thus, similar conditions were applied to phosphate (pH 8.0) and carbonate (pH 8.5) buffers (Figure 1E,F, respectively). The reaction in phosphate buffer/DMSO reached full conversion within 24 h without a decrease in the enantioselectivity of the major diastereoisomer compared to Tris buffer.

Since the desymmetrization of the racemic Wittig product ***rac*-2a** via enzymatic hydrolysis gave poor results, we studied a one-pot process where the first rearrangement reaction afforded an enantiomerically enriched rearranged product **2**. This was achievable by exploiting our earlier study where we used either an organocatalytic approach or a Ca^{2+}-catalyzed system in the [2,3]-Wittig rearrangement reaction (Scheme 2).[15] Having observed the inhibition of enzyme with

Scheme 2. Cyclopropenimine and Ca^{2+}-Catalyzed [2,3]-Wittig Rearrangement Reaction

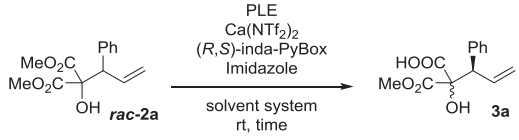


unacceptably low enantioselectivity (see Tables S3 and S4, SI) in a one-pot synthesis conducted using cyclopropenimine catalyst **I** in the first step, we moved on to the combination of the Ca^{2+}-catalyzed [2,3]-Wittig rearrangement reaction with hydrolysis.

Implementation of Ca^{2+}-Catalyzed [2,3]-Wittig Rearrangement/PLE-Mediated Desymmetrization in a One-Pot Reaction. First, an investigation of the Ca^{2+}-catalytic system compatibility with PLE-mediated hydrolysis was performed. In our earlier study,[15] Ca^{2+}-catalyzed [2,3]-Wittig rearrangement reactions were conducted in *i*PrOH. However, *i*PrOH caused transesterification of the starting material **1** and the intermediate **2**, which also participated in the hydrolysis step, thereby complicating the purification process of product **3**. To exclude the formation of these side products, we rescreened the solvents in the [2,3]-Wittig rearrangement reaction of **1a** to **2a**. As a result, MeOH showed equal activity to *i*PrOH, without the formation of any side products, although low enantioselectivity was observed (*i*PrOH showed 75% ee, and MeOH showed 24% ee; see Table S5, SI). Thus, to reach quantitative conversion and to avoid the formation of the transesterification products $Ca(NTf_2)_2$, (*R*,*S*)-inda-PyBox, and imidazole in MeOH were further used in the first step.

To this end, we carried out experiments to verify whether the Ca-inda-PyBox catalytic system used to perform the [2,3]-Wittig rearrangement reaction was compatible with PLE. For this, PLE-mediated hydrolysis was conducted in the selected solvent systems using the isolated racemic [2,3]-Wittig rearrangement reaction product ***rac*-2a** as a starting material in the presence of a catalytic amount of $Ca(NTf_2)_2$, (*R*,*S*)-inda-PyBox, and imidazole. The Tris buffer (pH 8.5)/$CHCl_3$ biphasic system was found to be ineffective by showing total inhibition of the enzyme activity (Table 1, entry 1; compare with Figure 1). We were delighted to find that PLE is sufficiently active in the phosphate buffer (Table 1, entries 2 and 3).

Table 1. Ca^{2+}-Catalytic System Compatibility with PLE[a]



entry	solvent system	time (h)	conversion (%)[b]	dr[c]	ee (%)[d] maj/min
1	Tris buffer (pH 8.5)/20% $CHCl_3$	72	7	n.d.[e]	n.d.[e]
2	phosphate buffer (pH 8.0)	24	75	7:1	13/99
3	phosphate buffer (pH 8.0)/20% DMSO	24	100	4:1	30/99

[a]Reaction conditions: 0.1 mmol scale, 5 mol % $Ca(NTf_2)_2$, 5 mol % (*R*,*S*)-inda-PyBox, 5 mol % imidazole, 85 EU of crude PLE, and the solvent system (0.2 M). [b]Conversion was determined by ^{1}H NMR analysis of the crude mixture and referred to the ratio of the starting material and the product. [c]Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. [d]Enantiomeric excess was determined by the chiral HPLC analysis of the sample obtained by preparative TLC; maj, major diastereoisomer and min, minor diastereoisomer. [e]n.d., not determined.

We then combined a Ca^{2+}-catalyzed [2,3]-Wittig rearrangement reaction and hydrolysis in a consecutive one-pot process. The results presented in Table 2 show the influence of the solvent system used in the second step on the rate and the selectivity of the one-pot reaction. During the one-pot synthesis, intermediate **2a** was not isolated, although solvent

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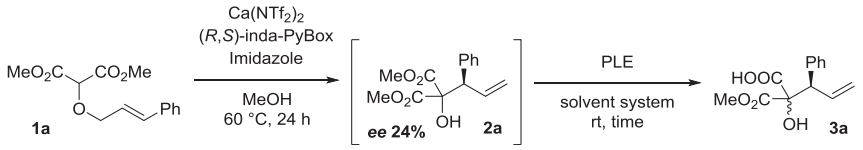
Table 2. Combination of a Ca^{2+}-Catalyzed [2,3]-Wittig Rearrangement Reaction with PLE-Mediated Hydrolysis in a One-Pot Reaction[a]



entry	solvent system	conversion (%)[b] 24 h	conversion (%)[b] 72 h	dr[c]	ee (%)[d] maj/min
1	carbonate buffer (pH 8.5)/20% $CHCl_3$	7	8	4.5:1	n.d.[e]
2	Tris buffer (pH 8.5)	69	81	6.3:1	51/95
3	Tris buffer (pH 8.5)/20% DMSO	78	83	4:1	64/96
4	carbonate buffer (pH 8.5)	47	86	3:1	64/99
5	carbonate buffer (pH 8.5)/20% DMSO	79[f]		4.3:1	59/99
6	carbonate buffer (pH 8.5)/20% DMSO (5 °C)	72[f]		4.5:1	57/99
7	phosphate buffer (pH 8.0)	36	46	7.6:1	63/99
8	phosphate buffer (pH 8.0)/20% DMSO	9	43	3.6:1	85/99
9	phosphate buffer (pH 8.0)/20% DMSO (35 °C)	100		2.9:1	73/99

[a]Reaction conditions: 0.1 mmol scale, 5 mol % $Ca(NTf_2)_2$, 5 mol % (*R*,*S*)-inda-PyBox, 5 mol % imidazole, and MeOH (0.1 M) were stirred at 60 °C for 24 h, followed by solvent evaporation and addition of 85 EU of crude PLE; solvent system (0.2 M). [b]Conversion was determined by ^{1}H NMR analysis of the crude mixture and referred to the ratio of starting material and the product. [c]Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. [d]Enantiomeric excess was determined by chiral HPLC analysis of the sample obtained by preparative TLC; maj, major diastereoisomer and min, minor diastereoisomer. [e]n.d., not determined. [f]Reaction conversion did not change after 2 h.

exchange was performed after the first step was complete (such a multistep process is still considered a one-pot reaction).[12,17] Hence, relying on our preliminary screening of buffers and co-solvents (see Table S2, SI; and Figure 1), we conducted the reactions in Tris (pH 8.5), carbonate (pH 8.5), and phosphate (pH 8.0) buffers. It was confirmed that the hydrolysis step could not be carried out in the biphasic system using a carbonate buffer (pH 8.5)/$CHCl_3$ solvent system (Table 2, entry 1). High conversion was achieved using Tris buffer (pH 8.5) without co-solvent as the reaction medium, as well as with DMSO, but in both cases product **3a** was formed in moderate enantioselectivity of the major diastereoisomer (ee 51 and 64%, respectively) (Table 2, entries 2 and 3). The reaction carried out in a carbonate buffer (pH 8.5) showed a moderate reactivity reaching 86% conversion in 72 h with the enantioselectivity of the major diastereoisomer of 64% (Table 2, entry 4). In addition to the enhancement of enzyme activity, higher diastereoselectivity was observed in the reaction utilizing DMSO as a co-solvent. However, it led to a lower ee of the major diastereoisomer (Table 2, entry 5). Surprisingly, a decrease in temperature did not influence the results obtained (Table 2, entry 6). The use of a phosphate buffer (pH 8.0) and a phosphate buffer (pH 8.0)/DMSO system decreased the rate of the reaction. However, promising enantioselectivity of the major diastereoisomer (85%) was detected (Table 2, entries 7 and 8). Therefore, by increasing the temperature to 35 °C, we were now able to run the one-pot reaction with full conversion (Table 2, entry 9).

To obtain a better understanding of the reaction, we decided to run the one-pot synthesis in optimal conditions and to follow the hydrolysis step using ^{1}H NMR. By monitoring the progress of the hydrolysis step (after the completion of the first step), we found that the reaction exhibited a sigmoidal curve leading to full conversion in 24 h (Figure 2a). For comparison, the kinetic study of the enzymatic reaction of isolated [2,3]-Wittig rearrangement product **2a** (ee 25%) was carried out under the same reaction conditions (Figure 2b). In this case, the reaction reached full conversion in 3 h. The presence of a lag phase and extended reaction time (Figure 2a) suggests that the inhibition of the enzyme occurred during the hydrolysis step in the one-pot reaction. However, it promotes the stereoselectivity of the reaction affording the major diastereoisomer in noticeably higher enantiomeric purity than in the case of the hydrolysis of the isolated [2,3]-Wittig rearrangement product **2a** (ee 73 and 52%, respectively).

Having successfully developed a one-pot procedure, the substrate scope was evaluated using $Ca(NTf_2)_2$, (*R*,*S*)-inda-PyBox, and imidazole in MeOH at 60 °C for the first step and PLE in a phosphate buffer (pH 8.0) with 20% of DMSO at 35 °C for the second step (Scheme 3). First, we used (*R*,*S*)- and (*S*,*R*)-inda-PyBox ligands for the consecutive one-pot reaction to gain access to both enantiomers of the rearrangement intermediate **2a**. In the case of intermediate (*S*)-**2a**, the hydrolysis step was slightly slower than expected compared to the hydrolysis with its enantiomer (*R*)-**2a**. Additionally, the enantiomeric excess of the major diastereoisomer of product **3a** from the reaction with intermediate (*S*)-**2a** dropped to 27% compared to 73% of *R*-enantiomer. From the obtained results it was clear that the PLE preferred *R*-enantiomer of compound **2a** providing notably higher ee of the major diastereoisomer in a shorter time; thus, the following one-pot reactions were carried out using (*R*,*S*)-inda-PyBox in the first step.

The aromatic substitution pattern in substrates **1a**−**i** did not affect the results of the [2,3]-Wittig rearrangement step substantially (full conversion was achieved in 24 h, and the ee of the intermediates **2a**−**i** were in the range 14−24%; detailed information in Table S7, SI), although the results of the hydrolysis step were dependent on it.

The hydrolysis step of *o*-chlorophenyl derivative **2b** was less efficient compared to the reaction with unsubstituted **2a** and reached only 56% of conversion in 48 h. Surprisingly, product **3b** was isolated with excellent diastereoselectivity but with low enantiomeric excesses of both diastereoisomers. Reactions with *m*- and *p*-chlorophenyl substituted intermediates **2c** and **2d**

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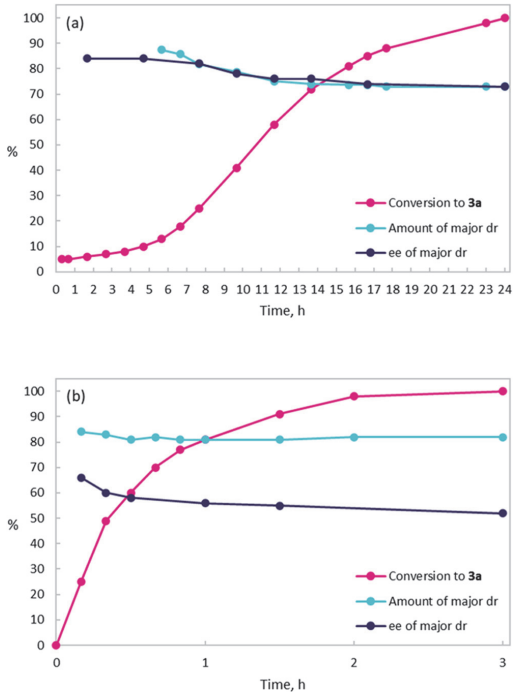

Figure 2. (a) Reaction profile for the hydrolysis step of the one-pot reaction without isolation of the [2,3]-Wittig rearrangement product **2a**. Enantiomeric excess of the minor diastereoisomer remained 99% during the reaction. (b) Reaction profile for the hydrolysis reaction using isolated [2,3]-Wittig rearrangement product **2a** as the starting material. Enantiomeric excess of the minor diastereoisomer remained 99% during the reaction.

stopped before reaching full conversion, affording products **3c** and **3d** with 68 and 64% yields, respectively. However, similar diastereo- and enantioselectivities were detected. Compounds **1e** and **1f** with electron-donating and electron-withdrawing substituents were tolerated under the reaction conditions, but in both cases, the hydrolysis step was slower. While the electron-donating substituent had no notable influence on the selectivities of the obtained product **3e**, the electron-withdrawing nitro group containing intermediate **2f** provided product **3f** with a diminished enantiomeric purity of both diastereoisomers. A significant decrease in the rate of the hydrolysis step was detected using bulkier naphthyl- and indole-substituted intermediates **2g** and **2h** instead of the phenyl substituent. Surprisingly, the naphthyl-derived product **3g** was obtained with even better selectivity, although in the case of the indole-derived product **3h**, the enantioselectivities of both diastereoisomers dropped drastically. It was assumed that due to variation in the spatial arrangement of the substituents (2-naphtyl and 1-indolyl), substrates fit the active site of the enzyme differently, which led to differences in enantioselectivity. When a heteroaromatic derivative **1i** was used as a starting material, a full conversion in the hydrolysis step was achieved within 24 h, resulting in product **3i** with higher diastereoselectivity (6.7:1), although, unfortunately, the enantiomeric purity of the major diastereoisomer decreased. In the case of crotyl-substituted substrate **1j**, an unreasonably long reaction time (7 days) was required for the [2,3]-Wittig rearrangement reaction. The conversion of the hydrolysis step reached a plateau at 93% in 24 h, but the one-pot product **3j** was isolated with a moderate 62% yield due to its instability during workup. The absence of the aromatic ring strongly affected the selectivities of the obtained product, leading to diminished diastereo- and enantioselectivities.

The rearrangement-hydrolysis protocol of other malonic esters was studied briefly. Due to the formation of transesterification products in the [2,3]-Wittig rearrangement step, the solvents were rescreened with substrates **1k** and **1l** (see Table S6, SI), indicating EtOH and *i*PrOH as the optimal solvents, respectively. The reaction with diethyl malonic derivative **1k** proceeded smoothly, providing half-ester **3k** with high diastereo- and enantioselectivities. In this case, higher enantioselectivity (ee 55%) of the intermediate **2k** was observed in the first step, which influenced the selectivities of the obtained one-pot product **3k**. Bulky dibenzyl derivative **1l** showed the highest enantioselectivity in the [2,3]-Wittig rearrangement, but unfortunately, only 17% of conversion was observed in the hydrolysis step within 72 h. The mixed ester **1m** did not reach full conversion in the first step even in 5 days; therefore, a mixture of the starting material **1m** and intermediate **2m** was used in the hydrolysis step leading to no reaction. The additional substituent in the double bond suppressed the reactivity of the starting material **1n**; thus, only 24% of conversion in the [2,3]-Wittig rearrangement reaction was detected.

Unfortunately, we were not able to determine the absolute configuration of product **3**. All our attempts to crystallize product **3** or amides derived from them using various solvent systems at different temperatures, slow evaporation technique, vapor diffusion method, seeding procedure, as well as co-crystallization and the crystalline sponge method with metal–organic frameworks[18] were unsuccessful. Also, we performed a conformational analysis and found that differences in energies of enantiomers were too small to determine the preferred configuration.

To show the synthetic utility of the proposed method, compound **3a** was converted into amide with benzylamine in the presence of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) in nearly quantitative yield (Scheme 4). The diastereoisomers of the obtained amide were chromatographically separable affording single enantiomers in high-to-very-high enantiomeric purities.

■ CONCLUSIONS

We developed an effective one-pot method by combining an asymmetric Ca^{2+}-catalyzed [2,3]-Wittig rearrangement reaction with an enzymatic desymmetrization of malonic esters. Such an implementation of the cascade catalysis in a one-pot manner provided access for the synthesis of vicinal quaternary and tertiary stereogenic centers containing α-hydroxy half-esters in high yields and good enantioselectivities. Different α-branched sterically demanding esters could be easily desymmetrized to the corresponding half-esters using the same one-pot procedure. Due to the compatibility of the Ca^{2+}-catalytic system with PLE, no isolation of the intermediate was required. In addition, the hydrolysis step is efficiently catalyzed by commercially available, crude PLE; thus, no expensive

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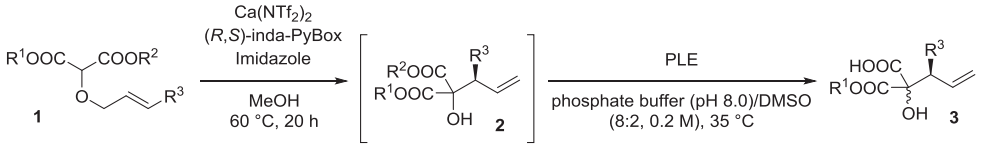
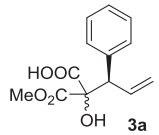
Scheme 3. Scope of the Reaction[a–l]



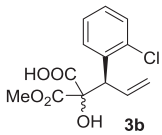
1a – 1l, 1n: $R^1 = R^2$ **2a – 2l, 2n**: $R^1 = R^2$



3a

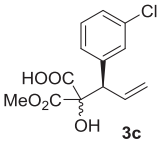
*via (R)-**2a***
yield 85%[b]
dr 2.9:1
ee 73%/99%

*via (S)-**2a***
yield 81%[c,d]
dr 1.6:1
ee 27%/99%



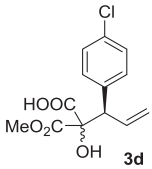
3b

yield 46%[d]
dr 20:1[e]
ee 31%/46%



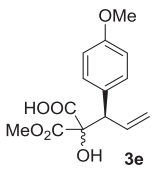
3c

yield 68%[b]
dr 2.6:1
ee 73%/99%



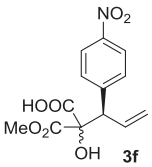
3d

yield 64%[b]
dr 2.9:1
ee 75%/96%



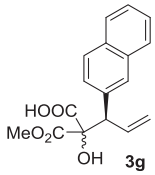
3e

yield 82%[d]
dr 2.5:1
ee 72%/97%



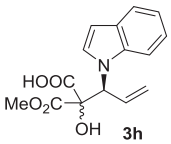
3f

yield 71%[d]
dr 2.7:1
ee 65%/91%



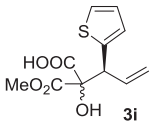
3g

yield 43%[d]
dr 2.6:1
ee 81%/99%



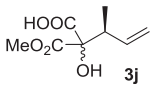
3h

yield 45%[d,f]
dr 3:1
ee 28%/39%



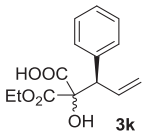
3i

yield 86%[b]
dr 6.7:1
ee 40%/99%



3j

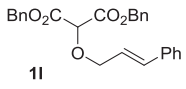
yield 62%[b,g]
dr 1.4:1
ee 64%/61%



3k

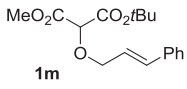
yield 46%[d,h]
dr 8:1
ee 73%/99%

limitations



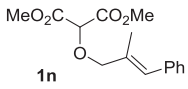
1l

step 1: conv 100%[i]
ee 78%
step 2: conv 17%[j]



1m

step 1: conv 85%[k]
dr 4.7:1
step 2: nr



1n

step 1: conv 24%[l]

[a]Reaction conditions: 0.3 mmol scale, 5 mol % $Ca(NTf_2)_2$, 5 mol % (*R*,*S*)-inda-PyBox, 5 mol % imidazole, and MeOH (0.1 M) were stirred at 60 °C for 20 h (if not stated otherwise), followed by solvent evaporation and addition of 255 EU of crude PLE, phosphate buffer (pH 8.0)/DMSO (8:2, 0.2 M). Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric excess was determined by chiral HPLC of the isolated product. Major diastereoisomers are depicted in the scheme. [b]Hydrolysis was completed after 24 h when the plateau phase was reached. [c](*S*,*R*)-Inda-PyBox was used. [d]Hydrolysis was completed after 48 h when the plateau phase was reached. [e]Diastereoisomeric ratio of the isolated product is presented. [f]Reaction was conducted in 0.1 mmol scale. [g]The [2,3]-Wittig rearrangement reaction was completed after 7 days. [h]The [2,3]-Wittig rearrangement reaction was conducted in absolute EtOH. [i]The [2,3]-Wittig rearrangement reaction was conducted in *i*PrOH. [j]Conversion of the hydrolysis was determined after 72 h. [k]The [2,3]-Wittig rearrangement reaction was stopped after 5 days. [l]Conversion of the [2,3]-Wittig rearrangement reaction was determined after 48 h.

purified isoenzyme forms nor modification of the enzyme were needed.

■ EXPERIMENTAL SECTION

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the one-dimensional (1D) and two-dimensional (2D) Fourier transform (FT) NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR), and DMSO-d_6 δ = 2.50 (^{1}H NMR), 39.52 (^{13}C NMR)] as internal standards. All peak assignments are confirmed by 2D experiments (^{1}H–^{1}H correlated spectroscopy (COSY), ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC), ^{1}H–^{13}C heteronuclear multiple bond correlation (HMBC)). In ^{13}C NMR, 2C in brackets refers to either two chemically equivalent or two overlapping unique carbon signals. The determination of the diastereomeric ratio in the reaction mixture was based on CH_2 integrals of the double bonds (^{1}H NMR in DMSO-d_6). If possible, the obtained ratio of diastereomers was also determined using the CH integrals of

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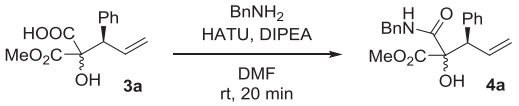
Scheme 4. Amidation of Compound 3a[a]



[a]Reaction conditions: 0.2 mmol scale, 1.1 equiv of $BnNH_2$, 1.1 equiv of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxid hexafluorophosphate (HATU), and 1.1 equiv of *N*,*N*-diisopropylethylamine (DIPEA) in DMF (0.1 M) were stirred at room temperature (rt) for 20 min. Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric excess was determined by chiral HPLC of the isolated diastereoisomers of product **4a**.

the double bonds or CHAr integrals. The determination of the diastereomeric ratio of the isolated products was based on $COOCH_3$ integrals (^{1}H NMR in $CDCl_3$). High-resolution mass spectra (HRMS) were recorded using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer and electrospray ionization (ESI). Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm) and Chiralcel OJ-H (250 × 4.6 mm) columns. In the case of carboxylic acids **3**, trifluoroacetic acid (TFA) was used as a mobile phase additive in chiral HPLC. Absolute ethanol (ABSE) was used as received. Precoated silica gel 60 F254 plates were used for TLC. Column chromatography was performed on a Biotage Isolera Prime preparative purification system with silica gel Kieselgel 40−63 μm. Purchased chemicals and solvents were used as received. Petroleum ether (PE) had a boiling point of 40−60 °C. Esterase from porcine liver (PLE, lyophilized powder; 18 units/mg, 20 units/mg, 24 units/mg) was purchased from Sigma-Aldrich. The reactions were performed under an air atmosphere without additional moisture elimination unless stated otherwise.

Ligands (*S*,*R*)- and (*R*,*S*)-inda-PyBox were prepared according to the literature procedures.[19]

Synthesis of Starting Materials 1a−n. Compounds **1a−g**, **1i**, and **1l** were synthesized according to the procedure previously described in the literature. The analytical data of compounds **1a−g**, **1i**, and **1l** are in agreement with the literature data.[15]

The same general procedure was used for the synthesis of compounds **1h**, **1j**, **1k**, **1m**, and **1n**, which is described below.

General Procedure. Rhodium(II) acetate dimer (0.005 equiv) and dichloromethane (DCM) (0.4 M) were added to an alcohol (1.2 equiv) under an argon atmosphere. The corresponding 2-diazomalonate (1 equiv) solution in DCM (0.4 M) was added for over 5 min at 0 °C. The reaction was stirred overnight at rt. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel.

Dimethyl (E)-2-((3-(1H-Indol-1-yl)allyl)oxy)malonate ***1h.*** Indole (1171 mg, 10 mmol) and sodium *tert*-butoxide (481 mg, 5 mmol) were added to DMF (63 mL, 0.16 M) under an argon atmosphere for 30 min. Then, ethyl propionate (1.21 mL, 12 mmol) was added for over 2 min, and the reaction was stirred for 4 h at rt. The solvent was removed under reduced pressure and the crude mixture was purified twice by column chromatography on silica gel (3−5% EtOAc in DCM and 30−65% DCM in PE), providing ethyl (*E*)-3-(1*H*-indol-1-yl)-acrylate (570 mg, 26%) as a dark yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 14.0 Hz, 1H), 7.64−7.56 (m, 2H), 7.38 (d, J = 3.5 Hz, 1H), 7.33 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.23 (ddd, J = 7.9, 7.2, 0.9 Hz, 1H), 6.73 (dd, J = 3.7, 0.8 Hz, 1H), 5.96 (d, J = 14.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). Analytical data are in agreement with the literature data.[20]

Diisobutylaluminum hydride (DIBAL-H) (1 M solution in toluene, 5.7 mL, 5.73 mmol) was added to an ethyl (*E*)-3-(1*H*-indol-1-yl)acrylate (561 mg, 2.61 mmol) solution in DCM (13 mL, 0.2 M) under an argon atmosphere at −78 °C. The reaction was stirred for 2 h at −78 °C. Then, the reaction mixture was quenched by 1 M aq HCl solution and extracted with DCM (6 × 15 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (3−8% EtOAc in DCM), providing (*E*)-3-(1*H*-indol-1-yl)prop-2-en-1-ol (247 mg, 55%) as a dark orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (m, 1H, Ar−C4), 7.50−7.45 (m, 1H, Ar−C7), 7.39 (d, J = 3.4 Hz, 1H, Ar−C2), 7.30−7.22 (m, 2H, CHAr and Ar−C6), 7.17 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H, Ar−C5), 6.63 (d, J = 3.4 Hz, 1H, Ar−C3), 5.92 (dt, J = 14.1, 6.6 Hz, 1H, $CHCH_2$), 4.36 (ddd, J = 6.7, 5.6, 1.3 Hz, 2H, CH_2OH), 1.47 (t, J = 5.7 Hz, 1H, OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.7, 129.2, 126.6, 124.0, 122.9, 121.4, 121.0, 112.1, 109.6, 105.3, 62.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}NO$ 174.0913; found 174.0905.

Following the general procedure, starting from (*E*)-3-(1*H*-indol-1-yl)prop-2-en-1-ol (289 mg, 1.67 mmol) and dimethyl 2-diazomalonate (220 mg, 1.39 mmol), the crude product was purified by column chromatography (2−8% EtOAc in PE/DCM 3/1 mixture), providing dimethyl (*E*)-2-((3-(1*H*-indol-1-yl)allyl)oxy)malonate **1h** (60 mg, 14%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dt, J = 7.9, 1.1 Hz, 1H, Ar−C4), 7.49−7.44 (m, 1H, Ar−C7), 7.38 (d, J = 3.5 Hz, 1H, Ar−C2), 7.31−7.23 (m, 2H, CHAr and Ar−C6), 7.17 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H, Ar−C5), 6.64 (d, J = 3.4 Hz, 1H, Ar−C3), 5.82 (dt, J = 14.2, 7.2 Hz, 1H, CH_2CH), 4.68 (s, 1H, OCH), 4.37 (dd, J = 7.1, 1.1 Hz, 2H, CH_2CH), 3.82 (s, 6H, $COOCH_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1 (2C), 135.6, 129.3, 129.1, 123.8, 123.1, 121.4, 121.2, 109.6, 106.8, 105.9, 77.4, 70.2, 53.1 (2C). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{17}NaNO_5$ 326.0999; found 326.0987.

Dimethyl (E)-2-(But-2-en-1-yloxy)malonate ***1j.*** Following the general procedure, starting from (*E*)-but-2-en-1-ol (185 mg, 2.57 mmol) and dimethyl 2-diazomalonate (338 mg, 2.14 mmol), the crude product was purified by column chromatography (2−8% EtOAc in PE/DCM 3/1 mixture), providing dimethyl (*E*)-2-(but-2-en-1-yloxy)malonate **1j** (176 mg, 41%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82−5.72 (m, 1H, $CHCH_3$), 5.62−5.53 (m, 1H, $CHCH_2$), 4.57 (s, 1H, OCH), 4.09 (dt, J = 6.6, 1.0 Hz, 2H, $CHCH_2$), 3.81 (s, 6H, $COOCH_3$), 1.75−1.69 (m, 3H, $CHCH_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3 (2C), 132.7, 125.8, 77.3, 71.9, 53.1 (2C), 17.9. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_9H_{14}NaO_5$ 225.0733; found 225.0735.

Diethyl 2-(Cinnamyloxy)malonate ***1k.*** Following the general procedure, starting from (*E*)-3-phenylprop-2-en-1-ol (259 mg, 1.93 mmol) and diethyl 2-diazomalonate (300 mg, 1.61 mmol), the crude product was purified by column chromatography (0−2% diethyl ether in toluene), providing diethyl 2-(cinnamyloxy)malonate **1k** (136 mg, 29%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.35−7.29 (m, 2H), 7.28−7.23 (m, 1H), 6.63 (d, J = 16.1

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Hz, 1H), 6.29 (dt, J = 15.8, 6.5 Hz, 1H), 4.59 (s, 1H), 4.34 (dd, J = 6.5, 1.2 Hz, 2H), 4.32−4.22 (m, 4H), 1.29 (t, J = 7.2 Hz, 6H). Analytical data are in agreement with the literature data.[21]

1-(tert-Butyl) 3-Methyl 2-(cinnamyloxy)malonate ***1m.*** To a solution of tosyl azide (374 mg, 1.89 mmol) and triethylamine (0.3 mL, 2.15 mmol) in acetonitrile (ACN) (1.72 mL, 1 M) was added *tert*-butyl methyl malonate (300 mg, 1.72 mmol) in ACN (1.72 mL, 1 M) at 0 °C. The reaction mixture was warmed to rt and stirred for 24 h. After evaporating the solvent, the crude mixture was purified by column chromatography on silica gel (3−7% EtOAc in PE) providing 1-(*tert*-butyl) 3-methyl 2-diazomalonate (279 mg, 81%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 1.51 (s, 9H). Analytical data are in agreement with the literature data.[22]

Following the general procedure, starting from (*E*)-3-phenylprop-2-en-1-ol (224 mg, 1.67 mmol) and 1-(*tert*-butyl) 3-methyl 2-diazomalonate (279 mg, 1.39 mmol), after evaporating the solvent, the crude mixture was purified by column chromatography on silica gel (3% EtOAc in PE/DCM 3/1 mixture). The impure fractions were repurified by column chromatography on silica gel (2−4% EtOAc in PE/DCM 3/1 mixture), providing 1-(*tert*-butyl) 3-methyl 2-(cinnamyloxy)-malonate **1m** (total yield: 203 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H, ArH), 7.35−7.29 (m, 2H, ArH), 7.28−7.22 (m, 1H, ArH), 6.63 (d, J = 15.9 Hz, 1H, CHAr), 6.29 (dt, J = 15.9, 6.4 Hz, 1H, CH_2CH), 4.50 (s, 1H, OCH), 4.37−4.28 (m, 2H, CH_2CH), 3.79 (s, 3H, $COOCH_3$), 1.48 (s, 9H, *t*Bu). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 165.7, 136.4, 134.7, 128.7 (2C), 128.2, 126.8 (2C), 124.3, 83.4, 78.3, 71.7, 52.8, 28.0 (3C). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_5$ 329.1359; found 329.1350.

Dimethyl (E)-2-((2-Methyl-3-phenylallyl)oxy)malonate ***1n.*** Following the general procedure, starting from (*E*)-2-methyl-3-phenylprop-2-en-1-ol (274 mg, 1.85 mmol) and dimethyl 2-diazomalonate (244 mg, 1.54 mmol), the crude mixture was purified by column chromatography (3−7% EtOAc in PE/DCM 3/1 mixture), providing dimethyl (*E*)-2-((2-methyl-3-phenylallyl)oxy)malonate **1n** (200 mg, 47%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 2H), 7.30−7.21 (m, 3H), 6.52 (s, 1H), 4.61 (s, 1H), 4.22 (d, J = 1.1 Hz, 2H), 3.82 (s, 6H), 1.93 (d, J = 1.4 Hz, 3H). Analytical data are in agreement with the literature data.[21]

General Procedure for the Chemoenzymatic One-Pot Synthesis of α-Hydroxy Half-Esters 3. To a solution of allyloxy 1,3-dicarbonyl compound **1** (0.3 mmol) in methanol (unless stated otherwise, 3 mL), $Ca(NTf_2)_2$ (0.015 mmol, 9 mg), (*R*,*S*)-inda-PyBox (0.015 mmol, 5.9 mg), and imidazole (0.015 mmol, 1 mg) were added. The reaction mixture was stirred at 60 °C until full conversion to the [2,3]-Wittig rearrangement product **2** was observed (^{1}H NMR). After evaporation of the solvent, the crude intermediate was suspended in DMSO (0.3 mL) and sodium phosphate buffer (pH 8.0, 1.2 mL). PLE (255 EU) was added, and the mixture was stirred at 35 °C until the plateau phase was reached. It was then acidified to pH 2 with 1 M aq HCl solution and extracted with diethyl ether (a drop of ethanol can be used to prevent emulsion formation). The combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the crude carboxylic acid was purified by column chromatography on silica gel (2% EtOAc in DCM (to elute the possible residual starting material), followed by 2% EtOAc in the DCM/formic acid 99/1 mixture), providing the desired product **3**. Since the diastereoisomers were chromatographically inseparable, a diastereomeric ratio after purification is shown. The enantioselectivities of intermediates **2** (see Table S7, SI) were determined by HPLC analysis according to the literature procedure[15] unless stated otherwise. The enantioselectivities were determined by HPLC analysis of the purified products **3**.

2-Hydroxy-2-(methoxycarbonyl)-3-phenylpent-4-enoic Acid ***3a.*** The title compound was synthesized following the general procedure from dimethyl 2-(cinnamyloxy)malonate **1a** (79 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. Compound **3a** was obtained as an off-white solid in 85% yield (64 mg); dr 2.9:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 73% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 39.0 min and t_R (minor) = 34.9 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H, ArH), 6.15 (ddd, J = 17.1, 10.2, 9.0 Hz, 1H, $CHCH_2$), 5.30−5.19 (m, 2H, CH_2), 4.32 (d, J = 9.0 Hz, 1H, CHAr), 3.69 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 137.3, 134.0, 129.0 (2C), 128.7 (2C), 128.0, 119.8, 83.1, 55.3, 54.3.

(3S)-Minor Diastereoisomer. ee 99% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 68.7 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.20 (m, 5H, ArH), 6.21−6.07 (m, 1H, $CHCH_2$), 5.22−5.17 (m, 2H, CH_2), 4.31 (d, J = 9.3 Hz, 1H, CHAr), 3.92 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 137.0, 134.7, 129.4 (2C), 128.6 (2C), 127.9, 119.1, 82.9, 55.2, 54.7.

HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{13}H_{13}O_5$ 249.0768; found 249.0772.

3-(2-Chlorophenyl)-2-hydroxy-2-(methoxycarbonyl)pent-4-enoic Acid ***3b.*** The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(2-chlorophenyl)allyl)oxy)malonate **1b** (90 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3b** was obtained as an off-white solid in 46% yield (39 mg); dr 20:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 31% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 9:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 16.3 min and t_R (minor) = 20.7 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7, 1.9 Hz, 1H, ArH), 7.37 (dd, J = 7.7, 1.6 Hz, 1H, ArH), 7.26−7.15 (m, 2H, ArH), 6.01 (ddd, J = 17.1, 10.1, 8.5 Hz, 1H, $CHCH_2$), 5.31−5.20 (m, 2H, CH_2), 5.09 (d, J = 8.5 Hz, 1H, CHAr), 3.66 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 169.8, 135.3, 134.1, 133.7, 130.1, 129.9, 128.9, 127.2, 120.1, 82.5, 54.3, 49.5.

(3S)-Minor Diastereoisomer. ee 46% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 9:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 26.0 min and t_R (minor) = 24.1 min].

HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{13}H_{12}ClO_5$ 283.0379; found 283.0384.

3-(3-Chlorophenyl)-2-hydroxy-2-(methoxycarbonyl)pent-4-enoic Acid ***3c.*** The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(3-

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chlorophenyl)allyl)oxy)malonate **1c** (90 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. Compound **3c** was obtained as a yellow solid in 68% yield (58 mg); dr 2.5:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 73% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 97:3, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 89.6 min and t_R (minor) = 118.9 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 1H, CCHCCl), 7.29−7.19 (m, 3H, ArH), 6.10 (ddd, J = 16.9, 10.2, 9.0 Hz, 1H, C*H*CH$_2$), 5.31−5.20 (m, 2H, CH$_2$), 4.30 (d, J = 9.0 Hz, 1H, CHAr), 3.72 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.7, 169.6, 139.4, 134.4, 133.5, 129.9, 129.2, 128.1, 127.2, 120.3, 82.8, 54.7, 54.4.

(3S)-Minor Diastereoisomer. ee 99% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 97:3, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 77.4 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.41 (m, 1H, CCHCCl), 7.29−7.19 (m, 3H, ArH), 6.12−6.00 (m, 1H, C*H*CH$_2$), 5.26−5.15 (m, 2H, CH$_2$), 4.29 (d, J = 9.4 Hz, 1H, CHAr), 3.91 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 169.4, 139.2, 134.3, 134.2, 129.85, 129.6, 128.0, 127.8, 119.6, 82.6, 54.8, 54.6.

HRMS (ESI) m/z: [M − H]$^-$ calcd for $C_{13}H_{12}ClO_5$ 283.0379; found 283.0383.

3-(4-Chlorophenyl)-2-hydroxy-2-(methoxycarbonyl)pent-4-enoic Acid ***3d***. The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(4-chlorophenyl)allyl)oxy)malonate **1d** (90 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. Compound **3d** was obtained as a white solid in 64% yield (55 mg); dr 2.4:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 75% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 97:3, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 35.1 min and t_R (minor) = 32.4 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 4H, ArH), 6.08 (ddd, J = 16.9, 10.2, 8.9 Hz, 1H, C*H*CH$_2$), 5.27−5.18 (m, 2H, CH$_2$), 4.29 (d, J = 8.9 Hz, 1H, CHAr), 3.68 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 169.6, 135.9, 133.9, 133.82, 130.4 (2C), 128.9 (2C), 120.0, 82.8, 54.4 (2C).

(3S)-Minor Diastereoisomer. ee 96% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 97:3, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 30.0 min and t_R (minor) = 22.2 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 4H, ArH), 6.10−5.99 (m, 1H, C*H*CH$_2$), 5.21−5.14 (m, 2H, CH$_2$), 4.28 (d, J = 9.3 Hz, 1H, CHAr), 3.89 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 169.9, 135.7, 134.4, 133.77, 130.9 (2C), 128.8 (2C), 119.4, 82.6, 54.7, 54.3.

HRMS (ESI) m/z: [M − H]$^-$ calcd for $C_{13}H_{12}ClO_5$ 283.0379; found 283.0383.

2-Hydroxy-2-(methoxycarbonyl)-3-(4-methoxyphenyl)-pent-4-enoic Acid ***3e***. The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(4-methoxyphenyl)allyl)oxy)malonate **1e** (88 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3e** was obtained as an off-white solid in 82% yield (69 mg); dr 2.5:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 72% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 50.2 min and t_R (minor) = 57.2 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.9 Hz, 2H, ArH), 6.83 (d, J = 8.9 Hz, 2H, ArH), 6.11 (ddd, J = 16.9, 10.2, 8.8 Hz, 1H, C*H*CH$_2$), 5.27−5.16 (m, 2H, CH$_2$), 4.28 (d, J = 8.8 Hz, 1H, CHAr), 3.78 (s, 3H, CH$_3$), 3.71 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 169.0, 159.24, 134.2, 130.0 (2C), 129.2, 119.5, 114.1 (2C), 83.2, 55.3, 54.6, 54.4.

(3S)-Minor Diastereoisomer. ee 97% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 61.9 min and t_R (minor) = 36.6 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.9 Hz, 2H, ArH), 6.86−6.80 (m, 2H, ArH), 6.14−6.05 (m, 1H, C*H*CH$_2$), 5.20−5.15 (m, 2H, CH$_2$), 4.26 (d, J = 9.5 Hz, 1H, CHAr), 3.92 (s, 3H, CH$_3$), 3.77 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.5, 170.2, 159.22, 134.8, 130.5 (2C), 128.9, 118.8, 114.05 (2C), 83.0, 55.3, 54.7, 54.5.

HRMS (ESI) m/z: [M − H]$^-$ calcd for $C_{14}H_{15}O_6$ 279.0874; found 279.0875.

2-Hydroxy-2-(methoxycarbonyl)-3-(4-nitrophenyl)pent-4-enoic Acid ***3f***. The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(4-nitrophenyl)allyl)oxy)malonate **1f** (93 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3f** was obtained as an off-white solid in 71% yield (63 mg); dr 2.7:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 65% [Chiralpak AD-H, hexane (TFA 0.01%)/ABSE/*i*PrOH = 95:4:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 84.7 min and t_R (minor) = 97.4 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 2H, ArH), 7.55 (d, J = 8.8 Hz, 2H, ArH), 6.17−6.02 (m, 1H, C*H*CH$_2$), 5.28−5.32 (m, 1H, CH$_2$), 5.28−5.25 (m, 1H, CH$_2$), 4.45 (d, J = 8.9 Hz, 1H, CHAr), 3.71 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.8, 169.3, 147.58, 145.0, 133.0, 130.1 (2C), 123.8 (2C), 120.9, 82.4, 54.5, 54.5.

(3S)-Minor Diastereoisomer. ee 91% [Chiralpak AD-H, hexane (TFA 0.01%)/ABSE/*i*PrOH = 95:4:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 76.4 min and t_R (minor) = 153.0 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.11 (m, 2H, ArH), 7.58 (d, J = 8.8 Hz, 2H, ArH), 6.17−6.02 (m, 1H, C*H*CH$_2$), 5.28−5.25 (m, 1H, CH$_2$), 5.25−5.22 (m, 1H, CH$_2$), 4.45 (d, J = 9.2 Hz, 1H, CHAr), 3.94 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.7, 169.6, 147.55, 144.7, 133.5, 130.5 (2C), 123.7 (2C), 120.4, 82.3, 54.9, 54.4.

HRMS (ESI) m/z: [M − H]$^-$ calcd for $C_{13}H_{12}NO_7$ 294.0619; found 294.0626.

2-Hydroxy-2-(methoxycarbonyl)-3-(naphthalen-2-yl)-pent-4-enoic Acid ***3g***. The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(naphthalen-2-yl)allyl)oxy)malonate **1g** (94 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3g** was obtained as an off-white solid in 43% yield (39 mg); dr 2.3:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 81% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 66.9 min and t_R (minor) = 60.1 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.72 (m, 4H, ArH), 7.50−7.39 (m, 3H, ArH), 6.25 (ddd, J = 17.2, 10.1, 8.7

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Hz, 1H, C*H*CH$_2$), 5.34−5.19 (m, 2H, CH$_2$), 4.51 (d, *J* = 8.8 Hz, 1H, CHAr), 3.64 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.9, 169.8, 134.9, 134.1, 133.5, 133.0, 128.3, 128.1, 128.0, 127.8, 126.9, 126.3, 126.23, 119.9, 83.2, 55.3, 54.3.

(3S)-Minor Diastereoisomer. ee 99% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 130.4 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89−7.72 (m, 4H, ArH), 7.59−7.39 (m, 3H, ArH), 6.33−6.15 (m, 1H, C*H*CH$_2$), 5.34−5.19 (m, 2H, CH$_2$), 4.50 (d, *J* = 9.2 Hz, 1H, CHAr), 3.93 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.4, 169.6, 134.8, 134.6, 133.4, 132.9, 128.6, 128.2, 128.18, 127.7, 127.3, 126.16 (2C), 119.2, 83.0, 55.1, 54.7.

HRMS (ESI) *m*/*z*: [M − H]$^-$ calcd for $C_{17}H_{15}O_5$ 299.0925; found 299.0928.

2-Hydroxy-3-(1H-indol-1-yl)-2-(methoxycarbonyl)pent-4-enoic Acid ***3h.*** The title compound was synthesized following the general procedure in a 0.1 mmol scale from dimethyl (*E*)-2-((3-(1*H*-indol-1-yl)allyl)oxy)malonate **1h** (35 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3h** was obtained as an off-white solid in 45% yield (15 mg); dr 2.6:1 (^{1}H NMR).

(3S)-Major Diastereoisomer. ee 28% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 47.9 min and t_R (minor) = 40.1 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (dt, *J* = 7.9, 1.0 Hz, 1H, Ar−C4), 7.47 (d, *J* = 8.4 Hz, 1H, Ar−C7), 7.38 (d, *J* = 3.4 Hz, 1H, Ar−C2), 7.25−7.19 (m, 1H, Ar−C6), 7.13−7.08 (m, 1H, Ar−C5), 6.54 (d, *J* = 3.3 Hz, 1H, Ar−C3), 6.16 (ddd, *J* = 17.2, 10.4, 7.0 Hz, C*H*CH$_2$), 5.95 (d, *J* = 6.7 Hz, 1H, CHAr), 5.38−5.26 (m, 2H, CH$_2$), 3.40 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 168.5, 168.4, 136.0, 130.4, 128.2, 126.1, 121.79, 121.2, 121.0, 120.0, 109.4, 103.4, 82.5, 61.1, 54.3.

(3R)-Minor Diastereoisomer. ee 39% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 61.1 min and t_R (minor) = 101.3 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H, Ar−C4), 7.51 (d, *J* = 8.2 Hz, 1H, Ar−C7), 7.48 (d, *J* = 3.3 Hz, 1H, Ar−C2), 7.23−7.16 (m, 1H, Ar−C6), 7.12−7.06 (m, 1H, Ar−C5), 6.52 (d, *J* = 3.3 Hz, 1H, Ar−C3), 6.17−6.06 (m, 1H, C*H*CH$_2$), 5.94 (d, *J* = 6.1 Hz, 1H, CHAr), 5.34−5.28 (m, 1H, CH$_2$), 5.20 (dt, *J* = 16.9, 1.1 Hz, 1H, CH$_2$), 3.94 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 168.8, 168.1, 136.6, 131.2, 128.2, 126.9, 121.77, 120.8, 120.6, 119.9, 109.9, 103.3, 82.3, 60.9, 54.5.

HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{15}NaNO_5$ 312.0842; found 312.0833.

2-Hydroxy-2-(methoxycarbonyl)-3-(thiophen-2-yl)pent-4-enoic Acid ***3i.*** The title compound was synthesized following the general procedure from dimethyl (*E*)-2-((3-(thiophen-2-yl)allyl)oxy)malonate **1i** (81 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 48 h. Compound **3i** was obtained as an off-white solid in 86% yield (66 mg); dr 6:1 (^{1}H NMR).

(3S)-Major Diastereoisomer. ee 40% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 93:7, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 33.4 min and t_R (minor) = 28.5 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (dd, *J* = 4.9, 1.5 Hz, 1H, ArH), 6.99−6.91 (m, 2H, ArH), 6.06 (ddd, *J* = 17.0, 10.1, 8.9 Hz, 1H, C*H*CH$_2$), 5.33−5.25 (m, 1H, CH$_2$), 5.22 (dd, *J* = 10.1 Hz, 1H, CH$_2$), 4.69 (d, *J* = 8.9 Hz, 1H, CHAr), 3.77 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.9, 169.4, 138.8, 134.0, 126.8, 126.5, 125.5, 119.8, 82.7, 54.5, 50.85.

(3R)-Minor Diastereoisomer. ee 99% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 93:7, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 59.9 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25−7.16 (m, 1H, ArH), 7.04−7.00 (m, 1H, ArH), 6.99−6.91 (m, 1H, ArH), 6.12−5.97 (m, 1H, C*H*CH$_2$), 5.33−5.16 (m, 2H, CH$_2$), 4.68 (d, *J* = 9.2 Hz, 1H, CHAr), 3.90 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.2, 169.7, 138.7, 134.7, 127.0, 126.7, 125.6, 119.2, 82.5, 54.6, 50.88.

HRMS (ESI) *m*/*z*: [M − H]$^-$ calcd for $C_{11}H_{11}O_5S$ 255.0333; found 255.0334.

2-Hydroxy-2-(methoxycarbonyl)-3-methylpent-4-enoic Acid ***3j.*** The title compound was synthesized following the general procedure from dimethyl (*E*)-2-(but-2-en-1-yloxy)-malonate **1j** (61 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 7 days, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. Compound **3j** was obtained as a yellow oil in 62% yield (35 mg); dr 1.4:1 (^{1}H NMR).

(3S)-Major Diastereoisomer. ee 64% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 93:7, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 30.5 min and t_R (minor) = 18.9 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.77−5.67 (m, 1H, C*H*CH$_2$), 5.24−5.11 (m, 2H, CH$_2$), 3.91 (s, 3H, COOCH$_3$), 3.25−3.12 (m, 1H, C*H*CH$_3$), 1.02 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 171.0, 170.6, 136.2, 118.4, 82.33, 54.4, 43.9, 14.37.

(3R)-Minor Diastereoisomer. ee 61% [Chiralpak AD-H, hexane (TFA 0.01%)/*i*PrOH = 93:7, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 25.0 min and t_R (minor) = 22.0 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.67−5.59 (m, 1H, C*H*CH$_2$), 5.19−5.07 (m, 2H, CH$_2$), 3.86 (s, 3H, COOCH$_3$), 3.25−3.12 (m, 1H, C*H*CH$_3$), 1.09 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.7, 170.5, 136.6, 118.0, 82.26, 54.4, 44.3, 14.43.

HRMS (ESI) *m*/*z*: [M − H]$^-$ calcd for $C_8H_{11}O_5$ 187.0612; found 187.0615.

2-(Ethoxycarbonyl)-2-hydroxy-3-phenylpent-4-enoic Acid ***3k.*** HPLC analysis conditions for the [2,3]-Wittig rearrangement intermediate **2k**: ee 55% [Chiralpak AD-H, hexane/ABSE/*i*PrOH = 95:3:2, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 12.0 min and t_R (minor) = 10.8 min].

The title compound was synthesized following the general procedure from diethyl 2-(cinnamyloxy)malonate **1k** (88 mg). After 20 h, full conversion was achieved in the [2,3]-Wittig rearrangement reaction conducted in ethanol, then the enzymatic hydrolysis reaction mixture was stirred for 48 h. Compound **3k** was obtained as an off-white solid in 85% yield (68 mg); dr 8.3:1 (^{1}H NMR).

(3R)-Major Diastereoisomer. ee 73% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 19.2 min and t_R (minor) = 23.9 min]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41−7.33 (m, 2H, ArH), 7.32−7.22 (m, 3H, ArH), 6.15 (ddd, *J* = 17.1, 10.0, 9.0 Hz, 1H, C*H*CH$_2$), 5.29−5.23 (m, 1H, CHCH$_2$), 5.21 (dd, *J* = 10.1 Hz, 2.1 Hz, 1H, CHCH$_2$), 4.33 (d, *J* = 8.9 Hz, 1H, CHAr), 4.11 (q, *J* = 7.0 Hz, 2H, CH$_2$CH$_3$), 1.16 (t, *J* = 7.2 Hz,

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3H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.1, 169.3, 137.4, 134.4, 129.2 (2C), 128.6 (2C), 127.9, 119.5, 82.8, 64.1, 55.1, 13.9.

(3S)-Minor Diastereoisomer. ee 99% [Chiralpak OJ-H, hexane (TFA 0.01%)/*i*PrOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 29.7 min]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.33 (m, 2H, ArH), 7.32−7.22 (m, 3H, ArH), 6.18−6.08 (m, 1H, $CHCH_2$), 5.25−5.17 (m, 2H, $CHCH_2$), 4.37 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.32 (d, J = 9.4 Hz, 1H, CHAr), 1.38 (t, J = 7.2 Hz, 3H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.0, 169.9, 137.2, 134.6, 129.4 (2C), 128.6 (2C), 127.8, 119.1, 82.5, 64.4, 55.0, 14.2.

HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{14}H_{15}O_5$ 263.0925; found 263.0926.

*1 mmol Scale Chemoenzymatic One-Pot Synthesis of 2-Hydroxy-2-(methoxycarbonyl)-3-phenylpent-4-enoic Acid **3a**.* The experiment was conducted following the general procedure in a 1 mmol scale from dimethyl 2-(cinnamyloxy)-malonate **1a** (264 mg, 1 mmol). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. Compound **3a** was obtained as an off-white solid in 83% yield (208 mg); dr 2.2:1 (^1H NMR), ee 76/99% (HPLC).

General Procedure for the Synthesis of Racemic α-Hydroxy Half-Esters 3a−k. To a solution of allyloxy 1,3-dicarbonyl compound **1** (1 equiv) in $CHCl_3$ (0.2 M), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.2 equiv) was added. After stirring at rt for 5 min, the solvent was evaporated. The crude mixture was purified by column chromatography on silica gel (4−10% EtOAc in PE/DCM 3/1) providing racemic homoallyl alcohol **2**.

To a solution of homoallyl alcohol **2** (1 equiv) in MeOH (0.1 M), KOH (1 equiv) was added. The reaction mixture was stirred at rt until the completion of the reaction, monitored by TLC. Then, the pH of the mixture was adjusted to 9−10 using 1 M aq NaOH solution and extracted twice with diethyl ether. The water layer was then acidified to pH 2 with 1 M aq HCl solution and extracted with diethyl ether. The combined organic layers (extracted at pH 2) were dried over $MgSO_4$. Evaporation of the solvent provided the racemic product **3**. If necessary, additional purification by column chromatography was performed using 2% EtOAc in DCM/formic acid 99/1 mixture.

*Methyl 2-(Benzylcarbamoyl)-2-hydroxy-3-phenylpent-4-enoate **4a**.* To a solution of 2-hydroxy-2-(methoxycarbonyl)-3-phenylpent-4-enoic acid **3a** (50 mg, 0.2 mmol, dr 2.9:1) and HATU (84 mg, 0.22 mmol) in DMF (2 mL, 0.1 M), DIPEA (38 μL, 0.22 mmol) and benzylamine (24 mg, 0.22 mmol) were added. The reaction was stirred for 20 min at rt. Then, the reaction mixture was extracted once with distilled water and EtOAc. The organic phase was collected, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude mixture was purified twice by column chromatography on silica gel (5−20% EtOAc in PE), providing the major diastereoisomer (46 mg, 68%) and the minor diastereoisomer (18 mg, 27%) of compound **4a** as white solids.

(3R)-Major Diastereoisomer. ee 72% [Chiralpak AD-H, hexane/*i*PrOH = 9:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 19.1 min and t_R (minor) = 22.2 min]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, J = 5.9 Hz, 1H, NH), 7.37−7.20 (m, 10H, Ar), 6.11 (ddd, J = 17.1, 10.2, 8.8 Hz, 1H, $CHCH_2$), 5.19 (dt, J = 17.1, 1.3 Hz, 1H, $CHCH_2$), 5.14 (dd, J = 10.3, 1.6 Hz, 1H, $CHCH_2$), 4.56 (dd, J = 14.8, 6.3 Hz, 1H, $NHCH_2Ar$), 4.37 (d, J = 8.8 Hz, 1H, CHAr), 4.36 (dd, J = 14.8, 5.5 Hz, 1H, $NHCH_2Ar$), 4.29 (s, 1H, OH), 3.64 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 167.5, 138.3, 137.7, 134.8, 129.1 (2C), 128.8 (2C), 128.5 (2C), 128.0 (2C), 127.8, 127.6, 118.9, 82.9, 55.5, 54.0, 44.0.

(3S)-Minor Diastereoisomer. ee 99% [Chiralpak AD-H, hexane/*i*PrOH = 9:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm; t_R (major) = 15.5 min]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H, CH-*m*-Ar), 7.31−7.25 (m, 4H, CH-*o*-Ar, CH-*p*-Ar, $NHCH_2$-*p*-Ar), 7.21−7.14 (m, 2H, $NHCH_2$-*o*-Ar), 7.12−7.01 (m, 1H, NH), 6.76−6.64 (m, 2H, $NHCH_2$-*m*-Ar), 6.14 (dt, J = 17.1, 9.9 Hz, 1H, $CHCH_2$), 5.21 (ddd, J = 17.1, 1.6, 0.8 Hz, 1H, $CHCH_2$), 5.15 (dd, J = 10.2, 1.8 Hz, 1H, $CHCH_2$), 4.40 (dd, J = 15.0, 7.3 Hz, 1H, $NHCH_2Ar$), 4.38 (s, 1H, OH), 4.39−4.33 (m, 1H, CHAr), 4.00 (dd, J = 15.0, 4.6 Hz, 1H, $NHCH_2Ar$), 3.92 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 167.1, 137.9, 137.4, 135.6, 129.7 (2C), 128.6 (2C), 128.4 (2C), 127.5 (2C), 127.4 (2C), 118.5, 83.0, 55.4, 54.5, 43.4.

HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}NO_4$ 340.1543; found 340.1536.

General Procedure for the Kinetic Study. *Reaction Profile for the Hydrolysis Step of One-Pot Reaction without Isolation of the [2,3]-Wittig Rearrangement Product **2a**.* The experiment was conducted following the general procedure for the chemoenzymatic one-pot synthesis of α-hydroxy half-esters **3**, starting from dimethyl 2-(cinnamyloxy)malonate **1a** (79 mg). After full conversion was achieved in the [2,3]-Wittig rearrangement reaction within 20 h, the enzymatic hydrolysis reaction mixture was stirred for an additional 24 h. During this period, samples were taken from the reaction mixture for ^1H NMR (20 μL in 600 μL DMSO-d_6) and HPLC (30 μL). HPLC samples were acidified to pH 2 with 1 M aq HCl solution and extracted with diethyl ether. Enantiomeric excess was determined by chiral HPLC analysis of the sample obtained by preparative TLC.

*Reaction Profile for the Hydrolysis Reaction Using Isolated [2,3]-Wittig Rearrangement Product **2a** as a Starting Material.* To a solution of dimethyl 2-(cinnamyloxy)-malonate **1a** (53 mg, 0.2 mmol) in methanol (2 mL), $Ca(NTf_2)_2$ (0.01 mmol, 6 mg), (*R*,*S*)-inda-PyBox (0.01 mmol, 3.9 mg), and imidazole (0.01 mmol, 0.7 mg) were added. The reaction mixture was stirred at 60 °C for 20 h. After evaporating the solvent, the crude mixture was purified by column chromatography on silica gel (3−7% EtOAc in PE/DCM 3/1 mixture), providing dimethyl (*R*)-2-hydroxy-2-(1-phenylallyl)malonate **2a** (48 mg, 91%) as a white solid. To a suspension of dimethyl (*R*)-2-hydroxy-2-(1-phenylallyl)-malonate **2a** (47 mg, 0.17 mmol, ee 26%) in DMSO (0.18 mL) and sodium phosphate buffer (pH 8.0, 0.71 mL), PLE (150 EU) was added, and the mixture was stirred at 35 °C for 3 h. During this period, samples were taken from the reaction mixture for ^1H NMR (20 μL in 600 μL DMSO-d_6) and HPLC (30 μL). HPLC samples were acidified to pH 2 with 1 M aq HCl solution and extracted with diethyl ether. Enantiomeric excess was determined by chiral HPLC analysis of the sample obtained by preparative TLC.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02973.

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Synthesis of starting compounds; optimization procedures; copies of ^{1}H and ^{13}C spectra; and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Christoffers, J.; Baro, A.; Werner, T. α-Hydroxylation of β-Dicarbonyl Compounds. *Adv. Synth. Catal.* **2004**, *346*, 143−151.

(2) (a) Yang, C.; Shen, H. C.; Wu, Z.; Chu, H. D.; Cox, J. M.; Balsells, J.; Crespo, A.; Brown, P.; Zamlynny, B.; Wiltsie, J.; et al. Discovery of Novel Oxazolidinedione Derivatives as Potent and Selective Mineralocorticoid Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4388−4392. (b) Yang, C.; Balsells, J.; Chu, H. D.; Cox, J. M.; Crespo, A.; Ma, X.; Contino, L.; Brown, P.; Gao, S.; Zamlynny, B.; et al. Discovery of Benzimidazole Oxazolidinediones as Novel and Selective Nonsteroidal Mineralocorticoid Receptor Antagonists. *ACS Med. Chem. Lett.* **2015**, *6*, 461−465. (c) Rubio, O. H.; Taouil, R.; Muñiz, F. M.; Monleón, L. M.; Simón, L.; Sanzd, F.; Morána, J. R. A molecular receptor selective for zwitterionic alanine. *Org. Biomol. Chem.* **2017**, *15*, 477−485.

(3) Selected references for enantioselective synthesis of α-hydroxy ketoesters: (a) Acocella, M. R.; Mancheno, O. G.; Bella, M.; Jørgensen, K. A. Organocatalytic Asymmetric Hydroxylation of β-Keto Esters: Metal-Free Synthesis of Optically Active anti-Diols. *J. Org. Chem.* **2004**, *69*, 8165−8167. (b) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. Chiral Brønsted Acid-Catalyzed Enantioselective r-Hydroxylation of β-Dicarbonyl Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 4562−4563. (c) Baidya, M.; Griffin, K. A.; Yamamoto, H. Catalytic Enantioselective O-Nitrosocarbonyl Aldol Reaction of β-Dicarbonyl Compounds. *J. Am. Chem. Soc.* **2012**, *134*, 18566−18569. (d) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. NHC-catalysed, chemoselective crossed-acyloin reactions. *Chem. Sci.* **2012**, *3*, 735−740. (e) Yao, H.; Lian, M.; Li, Z.; Wang, Y.; Meng, Q. Asymmetric Direct α-Hydroxylation of β-Oxo Esters Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchona Alkaloids. *J. Org. Chem.* **2012**, *77*, 9601−9608. (f) Zou, L.; Wang, B.; Mu, H.; Zhang, H.; Song, Y.; Qu, J. Development of Tartaric Acid Derived Chiral Guanidines and Their Application to Catalytic Enantioselective α-Hydroxylation of β-Dicarbonyl Compounds. *Org. Lett.* **2013**, *15*, 3106−3109.

(4) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T. A Dynamic Kinetic Asymmetric Transformation in the α-Hydroxylation of Racemic Malonates and Its Application to Biologically Active Molecules. *Angew. Chem., Int. Ed.* **2009**, *48*, 803−806.

(5) Wu, H.; Wang, Q.; Zhu, J. Catalytic Enantioselective Benzilic Ester Rearrangement. *Angew. Chem., Int. Ed.* **2020**, *59*, 7261−7265.

(6) Kano, T.; Song, S.; Maruoka, K. Molecular Recognition of Ketomalonates by Asymmetric Aldol Reaction of Aldehydes with Secondary-Amine Organocatalysts. *Chem. Commun.* **2012**, *48*, 7037−7039.

(7) Wang, C.; Zong, L.; Tan, C.-H. Enantioselective Oxidation of Alkenes with Potassium Permanganate Catalyzed by Chiral Dicationic Bisguanidinium. *J. Am. Chem. Soc.* **2015**, *137*, 10677−10682.

(8) Ha, M. W.; Choi, S.; Kim, S.; Lee, J. Y.; Lee, J. K.; Lee, J.; Hong, S.; Park, H. Phase-transfer catalyzed enantioselective α-alkylation of α-acyloxymalonates: construction of chiral α-hydroxy quaternary stereogenic centers. *RSC Adv.* **2016**, *6*, 77427−77430.

(9) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis: Regio- and Stereoselective Biotransformations*, 1st ed.; Wiley, 2005.

(10) Mohr, P.; Waespe-Šarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. A Study of Stereoselective Hydrolysis of Symmetrical Diesters with Pig Liver Esterase. *Helv. Chim. Acta* **1983**, *66*, 2501−2511.

(11) (a) Breznik, M.; Kikelj, D. Pig liver esterase catalyzed hydrolysis of dimethyl and diethyl 2-methyl-2-(o-nitrophenoxy)malonates. *Tetrahedron: Asymmetry* **1997**, *8*, 425−434. (b) Breznik, M.; Mrcina, A.; Kikelj, D. Enantioselective synthesis of (R)- and (S)-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamides. *Tetrahedron: Asymmetry* **1998**, *9*, 1115−1116. (c) Breznik, M.; Hrast, V.; Mrcina, A.; Kikelj, D. Stereoselective synthesis of (R)- and (S)-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acids, -carboxylates and -carboxamides. *Tetrahedron: Asymmetry* **1999**, *10*, 153−167. (d) Breznik, M.; Grdadolnik, S. G.; Giester, G.; Leban, I.; Kikelj, D. Influence of Chirality of the Preceding Acyl Moiety on the cis/trans Ratio of the Proline Peptide Bond. *J. Org. Chem.* **2001**, *66*, 7044−7050.

(12) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(13) (a) Denard, C. A.; Hartwig, J. F.; Zhao, H. Multistep One-Pot Reactions Combining Biocatalysts and Chemical Catalysts for Asymmetric Synthesis. *ACS Catal.* **2013**, *3*, 2856−2864. (b) Rudroff, F.; Mihovilovic, M. D.; Gröger, H.; Snajdrova, R.; Iding, H.; Bornscheuer, U. T. Opportunities and challenges for combining chemo- and biocatalysis. *Nat. Catal.* **2018**, *1*, 12−22.

(14) Selected references for combination of organocatalytic or metal-catalytic reactions with hydrolases in one-pot reaction: (a) Tenbrink, K.; Seßler, M.; Schatz, J.; Gröger, H. Combination of Olefin Metathesis and Enzymatic Ester Hydrolysis in Aqueous Media in a One-Pot Synthesis. *Adv. Synth. Catal.* **2011**, *353*, 2363−2367. (b) Pauly, J.; Gröger, H.; Patel, A. V. Catalysts Encapsulated in Biopolymer Hydrogels for Chemoenzymatic One-Pot Processes in Aqueous Media. *ChemCatChem* **2019**, *11*, 1503−1509.

(15) Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement. *J. Org. Chem.* **2017**, *82*, 2889−2897.

(16) Palomo, J. M.; Cabrera, Z. Enzymatic Desymmetrization of Prochiral Molecules. *Curr. Org. Synth.* **2012**, *9*, 791−805.

(17) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. A Simple Recipe for Sophisticated Cocktails: Organocatalytic One-Pot Reactions—Concept, Nomenclature, and Future Perspectives. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492−8509.

(18) Inokuma, Y.; Yoshioka, S.; Ariyoshi, J.; Arai, T.; Hitora, Y.; Takada, K.; Matsunaga, S.; Rissanen, K.; Fujita, M. X-ray analysis on the nanogram to microgram scale using porous complexes. *Nature* **2013**, *495*, 461−466.

(19) (a) Meng, J.-C.; Fokin, V. V.; Finn, M. G. Kinetic resolution by copper-catalyzed azide−alkyne cycloaddition. *Tetrahedron Lett.* **2005**, *46*, 4543−4546. (b) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. An Efficient and General One-Pot Method for the Synthesis of Chiral Bis(oxazoline) and Pyridine Bis(oxazoline) Ligands. *Synlett* **2005**, *15*, 2321−2324.

(20) Kabir, M. S.; Namjoshi, O. A.; Verma, R.; Lorenz, M.; Phani Babu Tiruveedhula, V. V. N.; Monte, A.; Bertz, S. H.; Schwabacher, A. W.; Cook, J. M. Base-Mediated Stereospecific Synthesis of Aryloxy and Amino Substituted Ethyl Acrylates. *J. Org. Chem.* **2012**, *77*, 300−310.

(21) Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. Synergistic Ion-Binding Catalysis Demonstrated via an Enantioselective, Catalytic [2,3]-Wittig Rearrangement. *ACS Cent. Sci.* **2016**, *2*, 416−423.

(22) Stokes, S.; Mustain, R.; Pickle, L.; Mead, K. T. Rhodium-catalyzed cyclopropanations of 2-aryl-2H-chromenes with dialkyl malonate esters. A comparison of α-diazo derivatives and phenyl-iodonium ylides. *Tetrahedron Lett.* **2012**, *53*, 3890−3893.

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Appendix 3

Publication III

Murre, A.; Mikli, V.; Erkman, K.; Kanger, T. Primary Amines as Heterogeneous Catalysts in an enantioselective [2,3]-Wittig rearrangement reaction. iScience **2023**, *26.*

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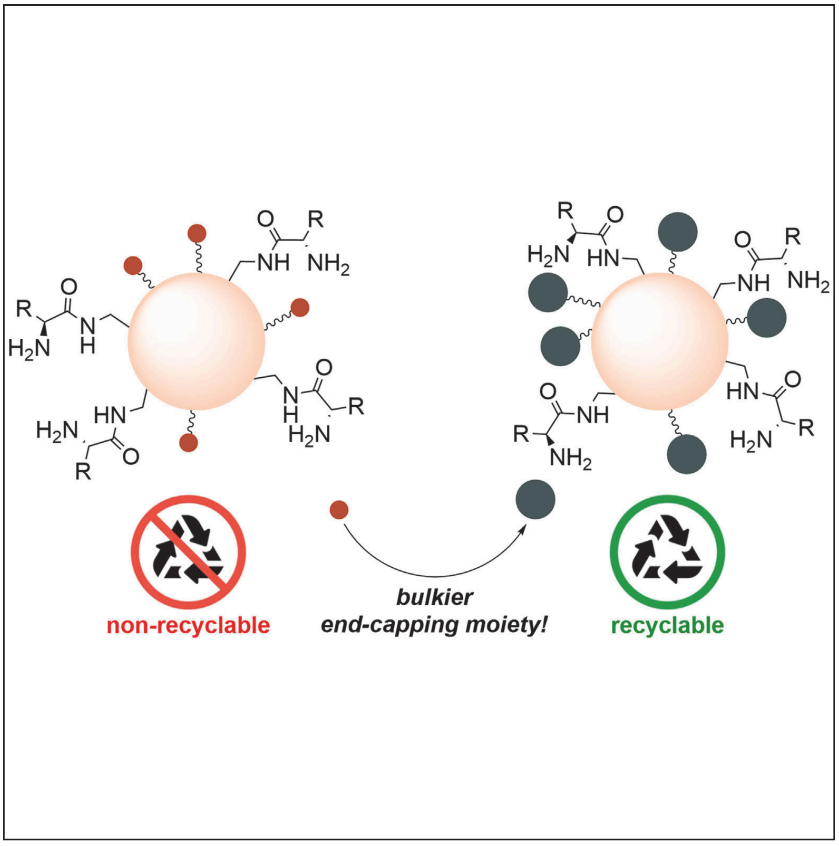
Primary amines as heterogeneous catalysts in an enantioselective [2,3]-Wittig rearrangement reaction



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Highlights

Chiral heterogeneous primary amino acid-derived catalysts were synthesized

Challenges related to the reusability of the catalytic system were resolved

The essential role of end-capping was showed as pivotal for achieving recyclability

Pivaloyl chloride was the most efficient reagent for the end-capping

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Primary amines as heterogeneous catalysts in an enantioselective [2,3]-Wittig rearrangement reaction

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SUMMARY

A series of heterogeneous catalysts anchored to different polystyrene-based supports has been prepared and applied in an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives. Among them, primary amino acid-derived (aminomethylated)polystyrene-supported catalysts showed excellent reactivity leading to the formation of rearranged products in good enantioselectivities of both diastereomers. Reusability issues connected to the deactivation of the catalyst were proved to be dependent on the end-capping strategy chosen for the blocking of the unreacted active sites of the resin. This issue of end-capping has not previously been in focus. Using bulkier pivaloyl end-capping moiety, we were able to recycle the catalyst in six consecutive cycles with only marginal deceleration of the reaction. Moreover, the epimerization of the product that occurred while conducting a rearrangement reaction in the presence of a homogeneous catalyst was almost fully eliminated by switching the catalytic system to heterogeneous.

INTRODUCTION

As sustainability becomes a viral concern, it creates challenges for constant improvement. Solutions to the problems connected with using large amounts of catalyst and the production of enormous quantities of waste must be found.[1,2] Heterogeneous catalysis provides a versatile opportunity to meet this goal.[3–5] The main benefit of using catalysts immobilized on solid support is the simplified isolation of the desired chiral product and convenient catalyst recovery using just a filtration/washing sequence.[6] Consequently, this makes the reaction setup less complex and, therefore, makes it possible to consider these reactions for manufacturing processes.[7–10] Since the pioneering work of the immobilization of proline onto a polymer support,[11] the field of the incorporation of chiral aminocatalysts on solid supports has begun to develop fast. Many examples are available for the successful use of both soluble and insoluble polymer-supported iminium-activation-based catalysts, especially prolines, imidazolidinones and their derivatives in different types of catalytic reactions.[12–16] However, the incorporation of chiral primary amines onto solid supports and their implementation as asymmetric catalysts are rather limited.[17–20] In addition, challenges associated with the reusability of the polymer-supported primary aminocatalysts sometimes arise, thereby narrowing their merits and application possibilities. The current study provides a deep insight into appeared recyclability issues and solutions for their elimination.

New carbon-carbon bond formation has always been one of the biggest challenges for organic chemists. Many synthetically useful reactions have been successfully developed and optimized to extend the carbon framework.[21] Well-known 100%-atom efficient rearrangement reactions are among the major tools used for this purpose.[22] A [2,3]-Wittig rearrangement reaction is a base-induced new C-C bond forming reaction occurring simultaneously with the breakage of a C-O bond (Scheme 1A).[23,24] In the case of ketones or aldehydes used as an electron-withdrawing group (EWG), a [2,3]-Wittig rearrangement reaction can also be promoted by enamine catalysis via increasing the nucleophilicity of the α-position of the EWG (Scheme 1B).[25]

Here, we introduce a successful and robust pathway for synthesis of cheap, easily accessible, and recyclable polystyrene-supported primary amines as catalysts and their application in the asymmetric [2,3]-Wittig rearrangement of cyclohexanone derivatives as an example of an efficient method for the synthesis of enantiomerically enriched homoallyl alcohols bearing two consecutive stereocenters.

RESULTS AND DISCUSSION

We have recently reported an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives.[26] Utilizing a structurally simple primary amine, substituted α-hydroxyketones were obtained with high yields, diastereoselectivities and enantioselectivities of the major diastereomer (Scheme 2). However, this approach is not devoid of limitations, since the epimerization of the rearrangement product happened

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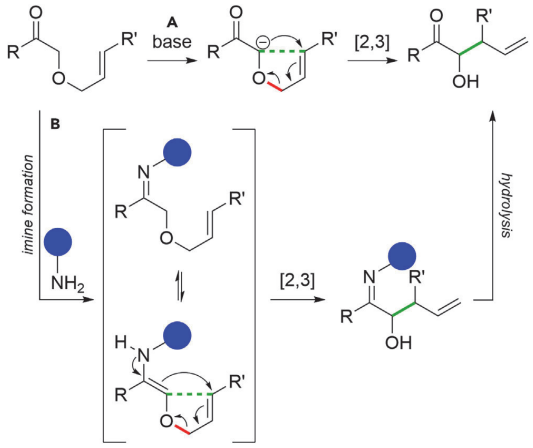


Scheme 1. [2,3]-Wittig rearrangement reaction promoted by base (A) or enamine catalysis (B)

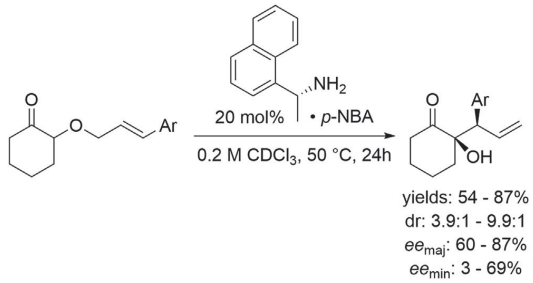
under the [2,3]-Wittig rearrangement conditions, diminishing enantioselectivity, especially drastically for the minor diastereomer. Additionally, high catalyst loading (20 mol %) is required for this reaction to be effective. Bearing in mind those problems and challenges, we decided to study whether a heterogeneous catalysis would help to overcome the limitations.

At the onset of the project, we considered different immobilization strategies of primary amines onto the divinylbenzene cross-linked polystyrene resins (Scheme 3, color codes were used throughout the article to differentiate solid supports). The incorporation of the organocatalysts onto the resin was easily followed by IR spectrometry and the loading of immobilized catalysts was estimated by the nitrogen content obtained from elemental analysis.

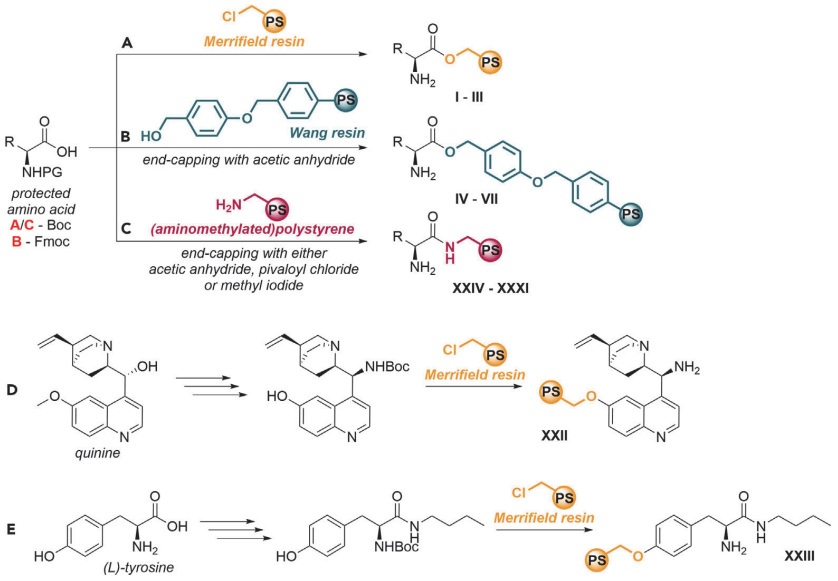
Firstly, a Merrifield resin was functionalized with protected α-amino acids in the presence of potassium fluoride. After the deprotection step catalysts **I–III** were obtained with 0.59–0.64 mmol/g loading range (Scheme 3A). To explore the effect of the linker length, the hydroxybenzotriazole (HOBt)/*N,N′*-diisopropylcarbodiimide (DIC)-catalyzed condensation of protected amino acids with a Wang resin was also used. It should be noted that, as the incorporation of organic molecules onto the resin is usually not full, functional groups of the resin may remain unreacted. Depending on the type of functionality, different blocking strategies are used to provide completely inert support.[27] Therefore, unreacted active sites of the resin were end-capped with acetic anhydride. Then, the protecting group of the amino acid part was removed yielding the formation of the ester-linked supported catalysts **IV–VII** (Scheme 3B).

In addition, a Boc-protected bulkier quinine derivative and tyrosine derivative were directly attached to the Merrifield resin via a nucleophilic substitution reaction in the presence of sodium hydride and potassium iodide, forming an ether bond, followed by the deprotection step. According to elemental analysis, the catalysts **XXII** and **XXIII** were isolated with loadings of 0.6 mmol/g and 0.34 mmol/g, respectively (Schemes 3D and 3E).

Finally, different protected α-amino acids were coupled with the (aminomethylated)polystyrene using peptide synthesis conditions. The remaining free primary amines of the resin were blocked using 3 different techniques; the reaction with acetic anhydride or pivaloyl chloride led to the formation of amides, and methyl iodide was used to prepare an alkylated resin. Removing the protecting group of the amino acid moiety provided the catalysts **XXIV–XXXI** with moderate loadings in the range of 0.38 mmol/g–0.59 mmol/g (Scheme 3C).[28]



Scheme 2. [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives; *p*-NBA – para-nitrobenzoic acid



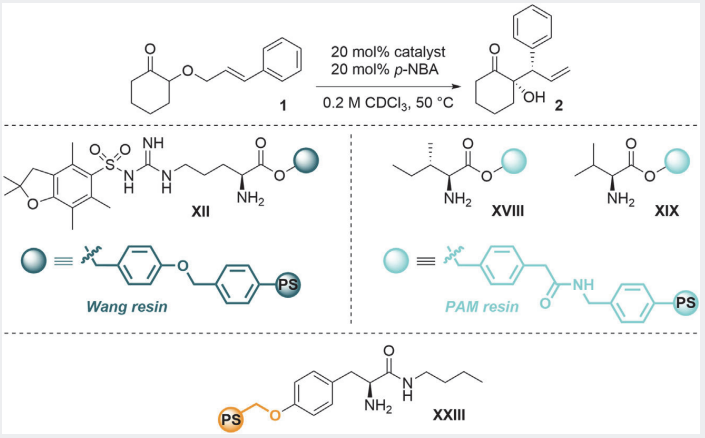
Scheme 3. Immobilization strategies of primary amines used in this work HOBt – hydroxybenzotriazole; DIC – N,N′-diisopropylcarbodiimide; DMAP – 4-dimethylaminopyridine

We started the investigation of the [2,3]-Wittig rearrangement of cyclohexanone derivatives under previously optimized reaction conditions for homogeneous catalysis with immobilized catalysts connected with the resin by an ester bond.[26] Reactions were carried out in $CDCl_3$ in the presence of a corresponding immobilized catalyst and a catalytic amount of *para*-nitrobenzoic acid (*p*-NBA). The reaction mixture was shaken in a temperature-controlled shaker at 50°C. The initial screening of the catalysts is represented in the supplementary information, Table S1. In this study, the series of both self-made (**I–VII**) and commercially available (**VIII–XXI**) catalysts (structures are available in supplementary information, Table S1) bonded to the Merrifield, Wang or *p*-hydoxymethylphenylacetamidomethyl polystyrene (PAM) resins through an ester moiety were tested showing sluggish catalytic efficiency. Even though, in some cases, full conversion was obtained, enantioselectivity remained low (up to 46%, See supplementary information, Table S1, entries 1–21). More importantly, our study revealed a major problem associated with the reusability of this type of catalysts, as already the second cycle of the recycling led to a diminished conversion and *ee*-s of the product (Table 1, entries 1–3).

Alternatively, a catalytic reaction was also conducted in toluene and acetonitrile. However, in both cases, the catalysts were still not recyclable (Table 1, entries 4–5). The possible leakage of the amino acid moiety from the resin was eliminated by elemental analysis, as the functionalization level (according to the nitrogen content) of the initial and recycled catalysts was nearly identical. To ascertain whether some structural changes in the catalyst happened during the rearrangement reaction, the IR spectra of reused catalysts were measured. This showed the appearance of an additional carbonyl band, suggesting intramolecular amidation of primary amine by the ester groups. It can happen either between primary amines of the catalysts and ester bonds formed during the end-capping of the corresponding catalysts with acetic anhydride or between two different units of amino acids bounded to the polymer matrix, not necessarily involving the end-capped ester moiety. Both scenarios led to the inactivation of the supported catalysts (Figure 1).

To prevent undesired blockage of the catalytic site, catalysts attached to the resin via an ether bond were used. Surprisingly, the catalyst **XXII**, made from a bulkier alkaloid, gave almost no reaction at all (See supplementary information, Table S1, entry 22). The tyrosine derivative **XXIII** showed moderate reactivity with very good enantioselectivity (88% for both major and minor diastereomers; See supplementary information, Table S1, entry 23). Unfortunately, the attempt to recycle the catalyst **XXIII** was unsuccessful (Table 1, entry 6). In the case of the catalyst **XXIII**, primary amines can be potentially alkylated by remaining unreacted chloride moieties on the resin (presence of the chlorine was confirmed by SEM), and that is why end-capping with NaOMe was conducted. However, this did not improve the reusability of the catalyst as a significant drop in both reactivity and selectivity was detected. As an elemental analysis and IR spectroscopy did not provide an explanation for such behavior, an additional morphological analysis was conducted. The mechanical degradation of the support material may also have been responsible for the shortening of the lifespan of the catalysts on the resin,[29–31] and this is why scanning electron microscopy (SEM) images of the initial (Figure 2A) and deactivated catalysts (Figure 2B) were obtained. SEM investigation was made with the help of Zeiss Field Emission Gun – Scanning Electron Microscope (FEG-SEM) Ultra-55. In Figure 2 high resolution mode at 4 kV accelerating voltage (AV) and In-lens SE detector was used. SEM images revealed no breakage of the polymer. Both catalysts appeared to be surface-wrinkled. The particle

Table 1. Recycling experiments for the [2,3]-Wittig rearrangement reaction of 1 with catalysts XII, XVIII, XIX, and XXIII



	Catalyst	I Cycle	Conv,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]	II Cycle	Conv,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XII		96	4.4:1	21	35		48	4.1:1	5	7
2	XVIII		78	2.9:1	39	38		15	2.7:1	23	19
3	XIX		62	2.9:1	46	46		5	ND	ND	
4[d]	XIX		58	3.3:1	58	56		16	2.6:1	14	8
5[e]	XIX		46	3.3:1	58	62		16	2.6:1	8	8
6	XXIII		44	3.5:1	88	88		12	3:1	44	50

p-NBA, *para*-nitrobenzoic acid; nd, not determined.
Reaction conditions: 0.1 mmol scale, solvent (0.5 mL). The major diastereomer is depicted in the scheme.
[a]The conversion was determined after 22 h by ^{1}H NMR of the crude reaction mixture.
[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).
[d]Toluene was used instead of $CDCl_3$.
[e]ACN was used instead of $CDCl_3$.

size is significantly smaller in deactivated catalyst (Figure 2A, scale 20 μm; Figure 2B, scale 10 μm) and their shape is a little irregular in the borders. This indicates a change in the matrix inner structure that can cause an impact in reaction outgoing.

As the tyrosine derivative **XXIII** gave rise to enantioselectivity of the desired product, we envisioned a cooperative effect between the amide proton and primary amine. Thus, we turned our attention to re-designing the immobilized catalysts. Consequently, series of catalysts **XXIV**–**XXVIIIa** attached through the carboxylic acid to the (aminomethylated)polystyrene were prepared (Scheme 3C).

Gratifyingly, the catalysts **XXIV**–**XXVIIIa** exhibited excellent catalytic performances with notable increase in the enantioselectivities (Table 2). The performance of immobilized organocatalysts was not significantly dependent on the side chain of the used amino acids, affecting mostly the diastereoselectivity of the obtained product.

As mentioned previously, the main advantage of heterogeneous catalysis is reusability. Thus, our next step was to explore the recyclability of the catalysts on the (aminomethylated)polystyrene. Unfortunately, the activity of both tested catalysts **XXVII** and **XXVIIIa** decreased drastically in the second cycle, leading to the diminished conversion of the reaction and the enantioselectivities of the rearrangement product. However, at the same time, this did not affect the diastereoselectivity (Table 3, entries 1 and 2). Next, the effect of the solvent nature and influence of the temperature on the performance of the reaction and, most importantly, on the reusability of the catalyst was studied (Table 3, entries 3–6). The obtained results revealed that catalysts recycled from the reactions performed in toluene or acetonitrile could still not be reused as significant drop in both reactivity and enantioselectivity was observed. However, even though the conversion of the reaction decreased by lowering the temperature, the recycled catalyst showed a smaller drop in reactivity. This observation suggested that structural changes in the catalyst by intramolecular side-reactions were decelerated at lower temperature. In order to explain this behavior, the IR spectra of the recycled catalysts were measured. The appearance of an additional band at the carbonyl region on the IR spectrum was detected, which correlates with the hypothesis of an intramolecular *trans*-amidation reaction happening between the primary amino groups of

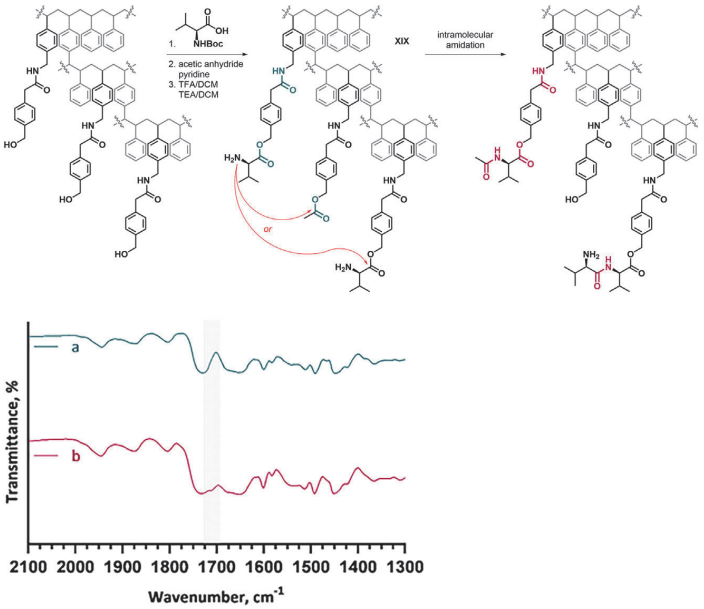


Figure 1. Deactivation of catalyst

(A and B) Plausible deactivation mechanism on the example of catalyst XIX and IR spectra of initial (A) and reused (B) catalyst **XIX**.

the catalyst and the end-capped amides of the resin under the [2,3]-Wittig rearrangement conditions. In an attempt to circumvent this drawback, two different end-capping methods were tested (Scheme 4).

In the catalyst **XXVIIIb**, the unreacted primary amines of the resin were end-capped with methyl iodide, yielding alkylated amines instead. Even though the catalyst performance in the second cycle was better than with the catalyst **XXVIIIa** (Table 3, entries 1 and 7), drop in both conversion and enantioselectivities was still observed. A solution to this problem was found using bulkier pivaloyl chloride for the end-capping of the unreacted primary amines on the resin, which provided the catalyst **XXVIIIc**. To our delight, the catalyst **XXVIIIc** showed the same reactivity as well as selectivities as the previously tested catalysts **XXVIIIa** and **XXVIIIb** in the first cycle, with remaining productivity in the second cycle (Table 3, entry 8).

Considering these findings, the catalysts **XXIX**–**XXXI** were additionally synthesized, following the same procedure as in the case of the catalyst **XXVIIIc**, utilizing the end-capping strategy with pivaloyl chloride. Of these, the catalysts **XXVIIIc** and **XXIX** showed the best catalytic performance, yielding rearrangement product **2** in full conversion with high enantiopurity (Table 4, entries 1 and 2). Notably, the catalyst **XXX**, with close structural similarity to the catalyst **XXIX**, led to the formation of product with disappointingly low enantioselectivities of both major and minor diastereomers (Table 4, entry 3). Such an outcome can be explained by the partial racemization of the catalyst. Due to the increased acidity of the benzylic α-proton of the phenylglycine, it is prone to racemize under the peptide synthesis conditions used to implement amino acid residue with the resin.[32] Surprisingly, a bulkier *tert*-butyl group at the α-position (the catalyst **XXXI**) did not improve the enantioselectivities of the product and, moreover, significantly decreased the diastereoselectivity (Table 4, entry 4). As additional optimization experiments using different solvents, temperature and amount of catalyst conducted with the catalyst **XXIX** did not show improvements in the reaction outcome, we proceeded with standard reaction conditions (See supplementary information, Table S2).

Once the catalysts with the higher catalytic performance (the catalysts **XXVIIIc** and **XXIX**) had been established, their robustness was tested with the recycling experiments (Figure 3; for detailed information see supplementary information, Table S3). After 22 h, an immobilized catalyst was separated from the reaction mixture by filtration, washed successively with chloroform and methanol, and dried. Then, the next experiment was carried out by the addition of a fresh batch of reagents and solvent to a sample of the recycled catalyst. The catalyst **XXVIIIc** was successfully reused four times without any loss in reactivity, affording product with constant diastereo- and enantioselectivities. However, surprisingly, a rapid drop in the activity of the mentioned catalyst was detected starting with the fifth cycle, also leading to a decrease in selectivities. We were pleased to find that the catalyst **XXIX** showed even better recyclability, leading to excellent catalytic performance in six consecutive cycles with only marginal erosion of conversion and enantioselectivities. The decrease in conversion became more significant in the seventh cycle and it continued to drop further after that (seventh cycle: 71% conversion after 16 h, eighth cycle: 48% conversion after 16 h); remarkably, however, there was no influence on the selectivities of the rearrangement product.

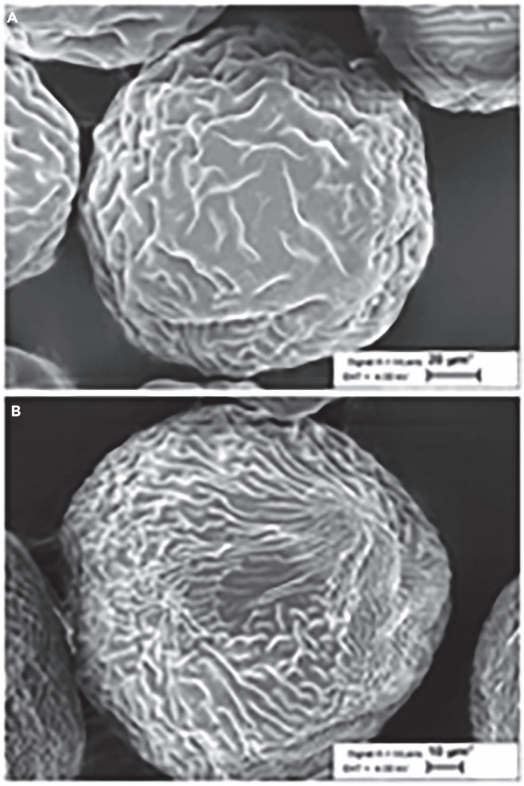


Figure 2. SEM images
(A and B) SEM images of initial (A) and deactivated (B) catalyst **XXIII**.

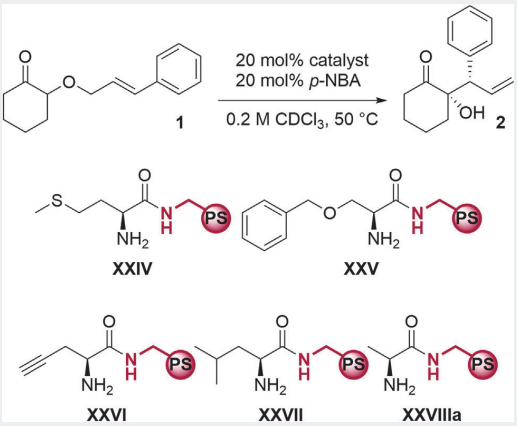
In order to elucidate the degradation of the catalyst, the IR was measured for the reused catalysts **XXVIIIc** and **XXIX** (Figure 4). As previously, the appearance of an additional carbonyl band on the IR spectra was noticed. However, only in the case of the reused catalysts **XXVIIIc** and **XXIX** did a peak at 2,245 cm^{-1} emerge. A plausible explanation for this is CO_2-induced carbamate formation from primary amine, ultimately resulting in catalyst deactivation.[33] The catalyst **XXIX** was also characterized by SEM using conventional Back-scattered imaging mode at 15 kV AV (Figure 5). We did not observe any substantial changes in the catalyst morphology.

While conducting the [2,3]-Wittig rearrangement reaction in the presence of a homogeneous catalyst, a noticeable drop in the enantioselectivity of the rearranged product was observed.[26] However, performing the same reaction using heterogeneous catalysis led to the formation of the product **2** with significantly higher enantioselectivity of both diastereomers (to compare, *ee* major/minor for product **2** with homogeneous catalysis – 77%/35%, heterogeneous catalysis – 86%/86%). The kinetic study of the [2,3]-Wittig rearrangement reaction of **1** with the immobilized catalyst **XXIX** revealed the full consumption of the starting material in 16 h. A decrease in *ee* of both diastereomers was also noticed, but, compared to the homogeneous catalysis, the detected drop was substantially smaller (Figure 6).

It is also worth mentioning that a simplified procedure for the isolation of the rearrangement product **2** can be applied. As a supported catalyst can be removed by filtration and the product is obtained free of any other contamination than a catalytic amount of *p*-NBA, basic extraction can be used to isolate pure product **2** in 84% yield.

In summary, different types of polystyrene-supported enantiomerically pure aminocatalysts were prepared. Among them, amino acids implemented onto the (aminomethylated)polystyrene afforded very good results in an asymmetric [2,3]-Wittig rearrangement reaction of cyclohexanone derivative **1**. The bulkiness of the end-capping moiety appeared to be critical for preserving the catalytic activity. The blocking of the unreacted primary amines of the resin with a pivaloyl group afforded immobilized catalysts that proved to be remarkably robust under the used reaction conditions, as demonstrated by recycling experiments. The catalyst **XXIX** demonstrated a high level of sustainability, as it could be recycled six times without significant deactivation. It is noteworthy that we have also shown that the isolation of the final product can be

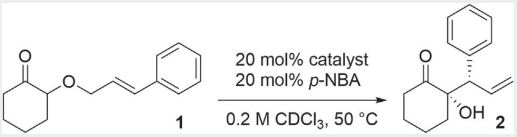
Table 2. Catalysts on (aminomethylated)polystyrene (end-capped with acetic anhydride) screening for the [2,3]-Wittig rearrangement reaction of 1



	Catalyst	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXIV	76	85	3.8:1	80	70
2	XXV	93	100	6:1	78	78
3	XXVI	69	82	5.1:1	92	84
4	XXVII	88	95	3.7:1	88	76
5	XXVIIIa	92	100	8.9:1	82	72

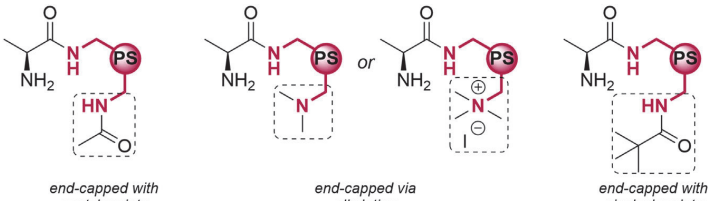
Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), *p*-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.
[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.
[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).

Table 3. Preliminary study on the recyclability of the catalysts on (aminomethylated)polystyrene



	Catalyst[a]	I Cycle	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]	II Cycle	Conv 16 h,%[a]	Conv 22 h,%[a]	*dr*[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXVIIIa		92	100	8.9:1	82	72		34	42	8.3:1	48	30
2	XXVII		88	95	3.7:1	88	76		25	31	3.7:1	56	38
3[d]	XXVIIIa		89	100	7:1	82	58		34	45	5.7:1	42	16
4[e]	XXVIIIa		84	96	6.8:1	74	46		27	35	5.9:1	25	6
5[f]	XXVIIIa		31	44	11.9:1	96	86		22	35	12.8:1	92	77
6[d,f]	XXVIIIa		29	40	9:1	94	74		19	34	7:1	88	63
7	XXVIIIb		93	100	8.6:1	87	73		60	73	8:1	70	50
8	XXVIIIc		88	100	8.6:1	86	71		91	100	8.4:1	82	65

Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), *p*-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.
[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.
[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c]The enantiomeric excess was determined by a chiral HPLC analysis of the sample obtained by preparative TLC.
[d]Toluene was used instead of $CDCl_3$.
[e]ACN was used instead of $CDCl_3$.
[f]Reaction was conducted at 35°C.



Scheme 4. End-capping methods applied in this work

performed following a simple filtration/extraction sequence without the use of column chromatography. This simplified work-up procedure allowed us to notably reduce the isolation time, making it more suitable for up-scaling.

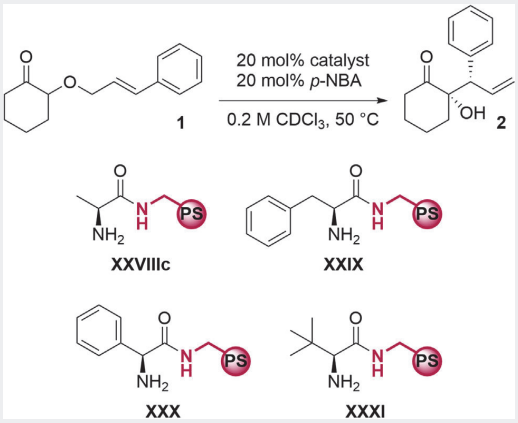
Limitations of the study

- Limitations associated with the scope of [2,3]-Wittig rearrangement of cyclohexanone derivatives can be found in our prior publication.[26]
- In this investigation, a heterogeneous catalyst with recyclability of up to six cycles is presented. Subsequent research is warranted to extend the reusability profile of the identified catalytic system.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

Table 4. Additional catalyst (end-capped by pivaloyl moiety) screening for the [2,3]-Wittig rearrangement reaction of 1



	Catalyst	Conv 16 h,%[a]	Conv 22 h,%[a]	dr[b]	ee_{maj},%[c]	ee_{min},%[c]
1	XXVIIIc	88	100	8.6:1	86	71
2	XXIX	100	–	3.2:1	86	86
3	XXX	74	83	5:1	24	22
4	XXXI	54	65	1.8:1	37	32

Reaction conditions: 0.1 mmol scale, catalyst (20 mol %), p-NBA (20 mol %), $CDCl_3$ (0.5 mL), 50°C.

[a]The conversion was determined by ^{1}H NMR of the crude reaction mixture.

[b]The diastereomeric ratio was determined by ^{1}H NMR of the crude product.

[c]The enantiomeric excess was determined by a chiral high-performance liquid chromatography (HPLC) analysis of the sample obtained by preparative thin-layer chromatography (TLC).

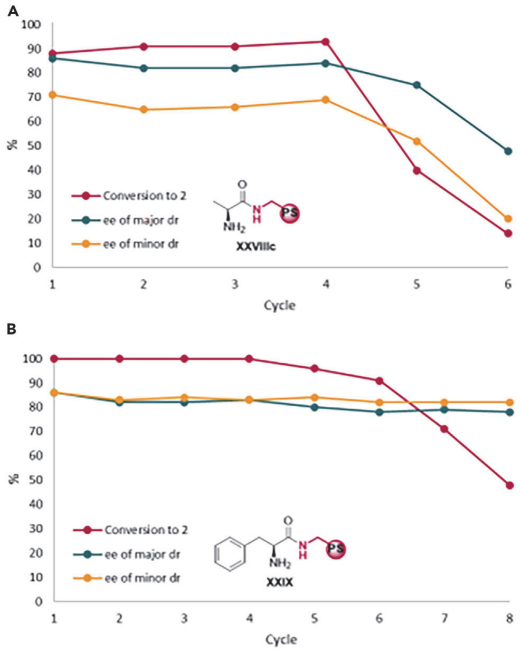


Figure 3. Recycling experiments

(A and B) Recycling experiments for the [2,3]-Wittig rearrangement reaction of 1 with catalysts **XXVIIIc** (A) and **XXIX** (B).

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- METHOD DETAILS

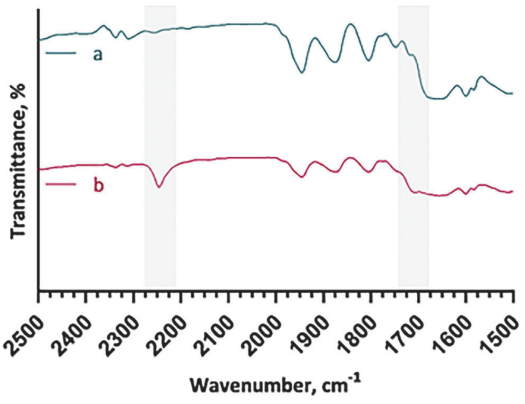


Figure 4. IR spectra

(A and B) IR spectra of freshly prepared (A) and reused (B) catalyst **XXIX**.

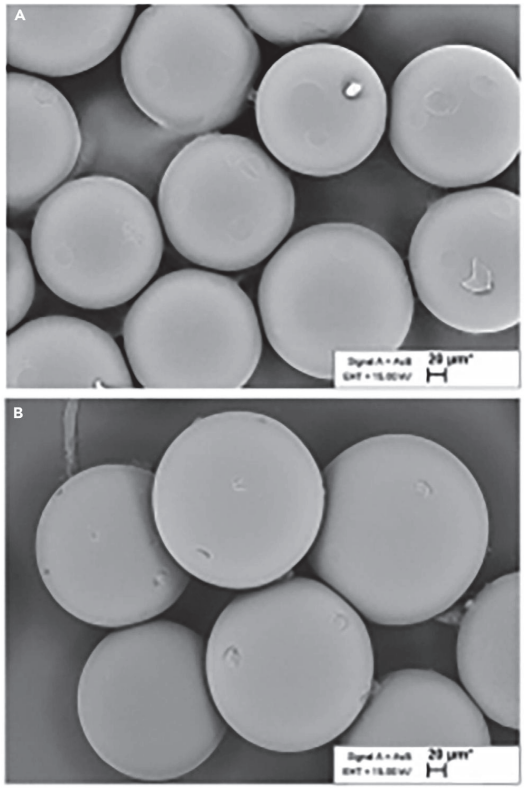


Figure 5. SEM images
(A and B) SEM images of initial (A) and deactivated (B) catalyst **XXIX**.

- Synthesis of the catalysts on the resin
- Recycling experiment

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107822.

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AUTHOR CONTRIBUTIONS

A.M. and K.E. conceived the project and conducted the synthesis. A.M. performed analysis and V.M. performed SEM analysis. All authors contributed to the discussion. A.M. and T.K. wrote the manuscript with contributions from all authors. T.K. supervised the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

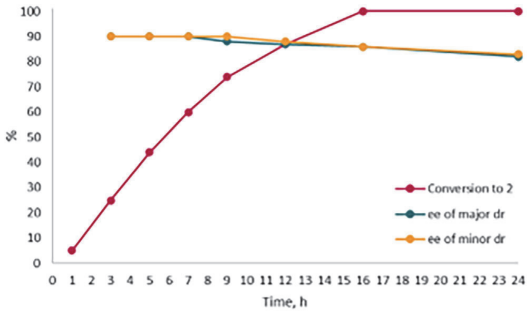

Figure 6. The reaction profile for the [2,3]-Wittig rearrangement reaction of 1 using the immobilized catalyst XXIX. The diastereoselectivity remained unchanged (3.2:1–3.3:1) during the reaction

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REFERENCES

1. Ayats, C., Henseler, A.H., Dibello, E., and Pericàs, M.A. (2014). Continuous Flow Enantioselective Three-Component *Anti*-Mannich Reactions Catalyzed by a Polymer-Supported Threonine Derivative. ACS Catal. *4*, 3027–3033. https://doi.org/10.1021/cs5006037.
2. Park, S.Y., Lee, J.-W., and Song, C.E. (2015). Parts-per-Million Level Loading Organocatalysed Enantioselective Silylation of Alcohols. Nat. Commun. *6*, 7512. https://doi.org/10.1038/ncomms8512.
3. Itsuno, S., and Hassan, M.M. (2014). Polymer-Immobilized Chiral Catalysts. RSC Adv. *4*, 52023–52043. https://doi.org/10.1039/C4RA09561H.
4. Itsuno, S., and Haraguchi, N. (2020). Catalysts Immobilized onto Polymers. In Catalyst Immobilization, M. Benaglia and A. Puglisi, eds. (Wiley), pp. 23–75. https://doi.org/10.1002/9783527817290.ch2.
5. Susam, Z.D., and Tanyeli, C. (2021). Recyclable Organocatalysts in Asymmetric Synthesis. Asian J. Org. Chem. *10*, 1251–1266. https://doi.org/10.1002/ajoc.202100165.
6. Alza, E., Sayalero, S., Kasaplar, P., Almaşi, D., and Pericàs, M.A. (2011). Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type Reactions. Chem. Eur J. *17*, 11585–11595. https://doi.org/10.1002/chem.201101730.
7. de Vos, D.E., Vankelecom, I.F.J., and Jacobs, P.A. (2000). Chiral Catalyst Immobilization and Recycling (Wiley-VCH).
8. Berkessel, A., and Gröger, H. (2005). Large-Scale Applications of Organocatalysis. In Asymmetric Organocatalysis (John Wiley & Sons, Ltd), pp. 393–408. https://doi.org/10.1002/3527604677.ch14.
9. Ding, K., and Uozumi, Y. (2008). Handbook of Asymmetric Heterogeneous Catalysis (Wiley-VCH).
10. Trindade, A.F., Gois, P.M.P., and Afonso, C.A.M. (2009). Recyclable Stereoselective Catalysts. Chem. Rev. *109*, 418–514. https://doi.org/10.1021/cr800200t.
11. Kondo, K., Yamano, T., and Takemoto, K. (1985). Functional Monomers and Polymers, 129. Asymmetric Robinson Cyclization Reaction Catalyzed by Polymer-Bound L-Proline. Makromol. Chem. *186*, 1781–1785. https://doi.org/10.1002/macp.1985.021860906.
12. Gruttadauria, M., Giacalone, F., and Noto, R. (2008). Supported Proline and Proline-Derivatives as Recyclable Organocatalysts. Chem. Soc. Rev. *37*, 1666–1688. https://doi.org/10.1039/B800704G.
13. Kristensen, T.E., and Hansen, T. (2010). Polymer-Supported Chiral Organocatalysts: Synthetic Strategies for the Road Towards Affordable Polymeric Immobilization. Eur. J. Org. Chem. *2010*, 3179–3204. https://doi.org/10.1002/ejoc.201000319.
14. Chiroli, V., Benaglia, M., Cozzi, F., Puglisi, A., Annunziata, R., and Celentano, G. (2013). Continuous-Flow Stereoselective Organocatalyzed Diels–Alder Reactions in a Chiral Catalytic "Homemade" HPLC Column. Org. Lett. *15*, 3590–3593. https://doi.org/10.1021/ol401390z.
15. Rodríguez-Escrich, C. (2020). Immobilized Chiral Organocatalysts. In Catalyst Immobilization, M. Benaglia and A. Puglisi, eds. (Wiley), pp. 217–256. https://doi.org/10.1002/9783527817290.ch7.
16. An, J.-X., Yang, F.-F., Wang, P., Gu, Z.-C., Li, Y., Chen, L., Zhao, Y.-L., and He, B. (2022). A Solid-Supported Organocatalyst for Asymmetric Mannich Reaction to Construct C2-Quaternary Indolin-3-Ones. RSC Adv. *12*, 7040–7045. https://doi.org/10.1039/D2RA00456A.
17. Izquierdo, J., and Pericàs, M.A. (2016). A Recyclable, Immobilized Analogue of Benzotetramisole for Catalytic Enantioselective Domino Michael Addition/Cyclization Reactions in Batch and Flow. ACS Catal. *6*, 348–356. https://doi.org/10.1021/acscatal.5b02121.
18. Henseler, A.H., Ayats, C., and Pericàs, M.A. (2014). An Enantioselective Recyclable Polystyrene-Supported Threonine-Derived Organocatalyst for Aldol Reactions. Adv. Synth. Catal. *356*, 1795–1802. https://doi.org/10.1002/adsc.201400033.
19. Porta, R., Coccia, F., Annunziata, R., and Puglisi, A. (2015). Comparison of Different Polymer- and Silica-Supported 9-Amino-9-Deoxy-Epi-Quinines as Recyclable Organocatalysts. ChemCatChem *7*, 1490–1499. https://doi.org/10.1002/cctc.201500106.
20. Cañellas, S., Ayats, C., Henseler, A.H., and Pericàs, M.A. (2015). A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow. ACS Catal. *7*, 1383–1391. https://doi.org/10.1021/acscatal.6b03286.
21. Wolfe, J.P. (2014). Carbon-Carbon σ-bond formation. In Comprehensive Organic Synthesis II, P. Knochel and A.G. Molander, eds. (Elsevier), pp. 1038–1072. https://doi.org/10.1016/B978-0-08-097742-3.00102-6.
22. Fleming, I. (2015). Pericyclic Reactions, 2nd Edition (Oxford University Press).
23. Nakai, T., and Mikami, K. (1994). The [2,3]-Wittig Rearrangement. In Organic Reactions, L.A. Paquette, ed. (John Wiley & Sons, Inc), pp. 105–209. https://doi.org/10.1002/0471264180.or046.02.
24. Nakai, T., and Mikami, K. (1986). [2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis. Chem. Rev. *86*, 885–902. https://doi.org/10.1021/cr00075a011.
25. Kimm, M., Ošeka, M., Kaabel, S., Metsala, A., Järving, I., and Kanger, T. (2019). [2,3]-Wittig Rearrangement as a Formal Asymmetric Alkylation of α-Branched Ketones. Org. Lett. *21*, 4976–4980. https://doi.org/10.1021/acs.orglett.9b01495.
26. Kimm, M., Järving, I., Ošeka, M., and Kanger, T. (2021). Asymmetric Organocatalytic [2,3]-Wittig Rearrangement of Cyclohexanone Derivatives. Eur. J. Org.

Chem. *2021*, 3113–3120. https://doi.org/10.1002/ejoc.202100435.

27. Ya-Ting Huang, A., Kao, C.-L., Selvaraj, A., and Peng, L. (2023). Solid-Phase Dendrimer Synthesis: A Promising Approach to Transform Dendrimer Construction. Mater. Today Chem. *27*, 101285. https://doi.org/10.1016/j.mtchem.2022.101285.
28. Karimov, R.R., Kazhkenov, Z.-G.M., Modjewski, M.J., Peterson, E.M., and Zhdankin, V.V. (2007). Preparation and Reactivity of Polymer-Supported 2-Iodylphenol Ethers, an Efficient Recyclable Oxidizing System. J. Org. Chem. *72*, 8149–8151. https://doi.org/10.1021/jo7015746.
29. Forni, J.A., Novaes, L.F.T., Galaverna, R., and Pastre, J.C. (2018). Novel Polystyrene-Immobilized Chiral Amino Alcohols as Heterogeneous Ligands for the Enantioselective Arylation of Aldehydes in Batch and Continuous Flow Regime. Catal. Today *308*, 86–93. https://doi.org/10.1016/j.cattod.2017.08.055.
30. Nascimento, D.L., Davy, E.C., and Fogg, D.E. (2018). Merrifield Resin-Assisted Routes to Second-Generation Catalysts for Olefin Metathesis. Catal. Sci. Technol. *8*, 1535–1544. https://doi.org/10.1039/C7CY02278F.
31. Oliveira, P.H.R., S Santos, B.M., Leão, R.A.C., Leão, R.A.C., San Gil, R.A.S., Souza, R.O.M.A., Finelli, F.G., and Finelli, F.G. (2019). From Immobilization to Catalyst Use: A Complete Continuous-Flow Approach Towards the Use of Immobilized Organocatalysts. ChemCatChem *11*, 5553–5561. https://doi.org/10.1002/cctc.201901129.
32. Liang, C., Behnam, M.A., Sundermann, T.R., and Klein, C.D. (2017). Phenylglycine Racemization in Fmoc-Based Solid-Phase Peptide Synthesis: Stereochemical Stability Is Achieved by Choice of Reaction Conditions. Tetrahedron Lett. *58*, 2325–2329. https://doi.org/10.1016/j.tetlet.2017.04.047.
33. Said, R.B., Kolle, J.M., Essalah, K., Tangour, B., and Sayari, A. (2020). A Unified Approach to CO2–Amine Reaction Mechanisms. ACS Omega *5*, 26125–26133. https://doi.org/10.1021/acsomega.0c03727.
34. Cassani, C., Martín-Rapún, R., Arceo, E., Bravo, F., and Melchiorre, P. (2013). Synthesis of 9-amino(9-deoxy)epi Cinchona Alkaloids, General Chiral Organocatalysts for the Stereoselective Functionalization of Carbonyl Compounds. Nat. Protoc. *8*, 325–344. https://doi.org/10.1038/nprot.2012.155.
35. Ranjbar, S., Riente, P., Rodríguez-Escrich, C., Yadav, J., Ramineni, K., and Pericàs, M.A. (2016). A. Polystyrene or Magnetic Nanoparticles as Support in Enantioselective Organocatalysis? A Case Study in Friedel–Crafts Chemistry. Org. Lett. *18*, 1602–1605. https://doi.org/10.1021/acs.orglett.6b00462.
36. Lorello, G.R., Legault, M.C.B., Rakić, B., Bisgaard, K., and Pezacki, J.P. (2008). Synthesis and Bioorthogonal Coupling Chemistry of a Novel Cyclopentenone-Containing Unnatural Tyrosine Analogue. Bioorg. Chem. *36*, 105–111. https://doi.org/10.1016/j.bioorg.2007.12.006.
37. Hupp, C.D., and Tepe, J.J. (2009). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride-Mediated Oxazole Rearrangement: Gaining Access to a Unique Marine Alkaloid Scaffold. J. Org. Chem. *74*, 3406–3413.
38. Cakici, M., Catir, M., Karabuga, S., Ulukanli, S., and Kilic, H. (2011). Synthesis and Asymmetric Catalytic Activity of (1S,1′S)-4,4′-Biquinazoline-Based Primary Amines. Tetrahedron: Asymmetry *22*, 300–308. https://doi.org/10.1016/j.tetasy.2011.01.009.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Deuterated chloroform	Deutero	Cas: 865-49-6
Dichloroethane	Penta	Cas: 107-06-2
Dichloromethane	Honeywell	Cas: 75-09-2
Toluene	Keemiakaubandus AS	Cas: 108-88-3
Acetonitrile	Honeywell	Cas: 75-05-8
Cyclopentyl methyl ether	Thermo Fischer Scientific	Cas: 5614-37-9
Methanol	Keemiakaubandus AS	Cas: 67-56-1
N,N-dimethylformamide	Thermo Fischer Scientific	Cas: 68-12-2
Isopropyl alcohol	Thermo Fischer Scientific	Cas: 67-63-0
Tetrahydrofuran	Thermo Fischer Scientific	Cas: 109-99-9
Diethyl ether	Honeywell	Cas: 60-29-7
Petroleum ether (bp: 40–60°C)	Honeywell	Cas: 8032-32-4
Ethyl acetate	Keemiakaubandus AS	Cas: 141-78-6
Hexane	Honeywell	Cas: 110-54-3
Trifluoroacetic acid	Apollo Scientific	Cas: 76-05-1
Triethylamine	Fisher Chemical	Cas: 121-44-8
Piperidine	Alfa Aesar	Cas: 110-89-4
Pyridine	Acros Organics	Cas: 110-86-1
4-dimethylaminopyridine	Acros Organics	Cas: 1122-58-3
Acetic anhydride	Reachim	Cas: 108-24-7
Para-nitrobenzoic acid	Honeywell	Cas: 62-23-7
Potassium fluoride	Sigma-Aldrich	Cas: 7789-23-3
Potassium carbonate	Lachner	Cas: 584-08-7
1-Hydroxybenzotriazole hydrate	Sigma-Aldrich	Cas: 123333-53-9
N,N′-diisopropylcarbodiimide	Sigma-Aldrich	Cas: 693-13-0
Triphenylphophine	Fluorochem	Cas: 603-35-0
Diisopropyl azodicarboxylate	Thermo Fisher Scientific	Cas: 2446-83-5
Diphenylphosphoryl azide	Sigma-Aldrich	Cas: 26386-88-9
Boron tribromide (1 M solution in DCM)	Sigma-Aldrich	Cas: 10294-33-4
Di-*tert*-butyl dicarbonate	Acros Organics	Cas: 24424-99-5
Iodine	Reachim	Cas: 7553-56-2
Sodium hydride (60% in mineral oil)	Sigma-Aldrich	Cas: 7646-69-7
Thionyl chloride	Acros Organics	Cas: 7719-09-7
Butyl amine	Sigma-Aldrich	Cas: 109-73-9
Pivaloyl chloride	Sigma-Aldrich	Cas: 3282-30-2
Methyl iodide	Sigma-Aldrich	Cas: 74-88-4
Boc-(L)-α-*tert*-butylglycine	Sigma-Aldrich	Cas: 62965-35-9
Boc-(L)-alanine	Orpegen	Cas: 15761-38-3
Boc-(L)-leucine	Alfa Aesar	Cas: 13139-15-6
Boc-*O*-benzyl-(L)-serine	Orpegen	Cas: 23680-31-1
Boc-(L)-methionine	Orpegen	Cas: 2488-15-5

(*Continued on next page*)

Continued

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Boc-(L)-2-propargylglycine	Sigma-Aldrich	Cas: 63039-48-5
Fmoc-(L)-phenylalanine	Sigma-Aldrich	Cas: 35661-40-6
Fmoc-(L)-isoleucine	Fluorochem	Cas: 71989-23-6
Fmoc-(L)-valine	Sigma-Aldrich	Cas: 68858-20-8
Fmoc-(L)-alanine	Orpegen	Cas: 35661-39-3
(L)-phenylalanine	Strem	Cas: 63-91-2
(L)-α-phenylglycine	Lancaster	Cas: 2935-35-5
Quinine	Sigma-Aldrich	Cas: 130-95-0
Merrifield resin LL	Sigma-Aldrich	*f* = 1.02 mmol/g, 100–200 mesh, 1% DVB
(Aminomethylated)polystyrene	Sigma-Aldrich	*f* = 1.2 mmol/g, 70–90 mesh, 1% DVB
Wang resin	Iris Biotech	*f* = 1.2 mmol/g, 100–200 mesh, 1% DVB
Software and algorithms		
ChemDraw Professional 20.0	PerkinElmer	https://www.perkinelmer.com/category/chemdraw

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Tõnis Kanger (tonis.kanger@taltech.ee).

Materials availability

All materials generated in this study are provided in the supplemental information.

IR spectra were obtained as potassium bromide pellets with a Bruker Tensor 27 FT-IR spectrophotometer. Elemental analyses were performed on Vario-Micro V2.2.0 CHNS analyzer. SEM was performed on Zeiss FEG-SEM Ultra-55. Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent signals were used [$CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR), MeOD δ = 3.31 (^{1}H NMR), 49 (^{13}C NMR), and DMSO-d6 δ = 2.50 (^{1}H NMR), 39.52 (^{13}C NMR)] as internal standards. The determination of the diastereomeric ratio in the reaction mixture was based on CH_2 integrals of the double bonds (^{1}H NMR in $CDCl_3$). The internal standard (1,3,5-trimethoxybenzene) was used to check whether NMR yields are in correspondence with observed conversions. There was no difference in obtained results and only conversions were determined after that. High-resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using ESI ionization. Chiral HPLC was performed by using Chiralcel OJ-H (250 × 4.6 mm) column. Optical rotations were obtained on an Anton Paar GWB Polarimeter MCP500 in abs.EtOH and calibrated with pure solvent as a blank. Column chromatography was performed on a Biotage Isolera Prime preparative purification system with silica gel Kieselgel 40−63 μm. Precoated silica gel 60 F254 plates were used for TLC. Purchased chemicals and solvents were used as received. EtOAc was distilled over phosphorus pentoxide. Petroleum ether (PE) had a boiling point of 40–60°C. Merrifield resin LL (*f* = 1.02 mmol/g, 100–200 mesh, 1% DVB) and (aminomethylated)polystyrene (*f* = 1.2 mmol/g, 70–90 mesh, 1% DVB, N elemental analysis (%): 1.69) were purchased from Sigma-Aldrich. Wang resin (*f* = 1.2 mmol/g, 100–200 mesh, 1% DVB) was purchased from Iris Biotech. The functionalization level of each catalyst was determined by elemental analysis. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

Represented work is based on our previous study of [2,3]-Wittig rearrangement reaction of cyclohexanone derivatives, where we have used homogeneous primary amines as catalyst.[26] In this article, we provide thorough discussion about scope and limitations of the reaction.

Data and code availability

- This study does not generate new unique reagent.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper can be obtained from the lead contact upon request.

METHOD DETAILS

Synthesis of the catalysts on the resin

General procedure for the deprotection of the Boc protected catalysts (GP I)

The Boc-protected catalyst on the resin (200 mg) was swollen in DCM (2 mL) for 20 min. DCM was then removed, 50% TFA solution in DCM (2 mL) was added and the reaction mixture was shaken at rt for 5 min. After filtration, resin was suspended in the fresh batch of 50% TFA solution in DCM (2 mL). After 20 min of shaking at rt, the solid was filtered and washed successively with IPA and DCM. 10% TEA solution in DCM (2 mL) was added and the reaction mixture was shaken at rt for 10 min. After filtration, resin was suspended in the fresh batch of 10% TEA solution in DCM (2 mL). After 10 min of shaking at rt, the solid was filtered and washed successively with IPA and DCM. The solid was dried in vacuo for 24 h.

General procedure (GPII) for the preparation of the immobilized catalysts I – III

Merrifield resin (200 mg, $f = 1.02$ mmol/g) was suspended in 1.5 mL DMF and allowed to swell for 20 min. Boc-protected amino acid (1.5 eq) and potassium fluoride (3 eq, 36 mg) were added to the suspension and the reaction mixture was shaken at 50°C for 24 h. The solid was filtered and washed successively with DMF, DMF:H_2O (1:1), MeOH:H_2O (1:1) and MeOH. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

Catalyst **I** was prepared according to the general procedure (GPII) starting from Boc-(L)-alanine (58 mg).
IR (KBr): ν 1732 cm^{-1} (carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.9, $f = 0.64$ mmol/g.
Catalyst **II** was prepared according to the general procedure (GPII) starting from Boc-(L)-leucine (71 mg).
IR (KBr): ν 1731 cm^{-1} (carbonyl band); 1718 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.82, $f = 0.59$ mmol/g.
Catalyst **III** was prepared according to the general procedure (GPII) starting from Boc-*O*-benzyl-(L)-serine (90 mg).
IR (KBr): ν 1736 cm^{-1} (carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing).
N elemental analysis (%): 0.85, $f = 0.61$ mmol/g.

General procedure (GPIII) for the preparation of the immobilized catalysts IV – VII

Wang resin (200 mg, $f = 1.2$ mmol/g) was suspended in 3 mL DCM/DMF (9:1) mixture of solvents and allowed to swell for 20 min. Fmoc-protected amino acid (2 eq), HOBt (2 eq, 65 mg), *N,N′*-diisopropylcarbodiimide (1 eq, 38 μL), and 4-dimethylaminopyridine (0.1 eq, 3 mg) were added to the suspension and the reaction mixture was shaken at rt for 3 h. Acetic anhydride (2 eq, 45 μL) and pyridine (2 eq, 39 μL) were then added to end-cap any unreacted hydroxyl groups on the resin and the reaction mixture was shaken at rt for additional 30 min. The solid was filtered and washed successively with DMF, DCM and MeOH. The solid was dried in vacuo for 24 h. The Fmoc-protected catalyst on the resin (200 mg) was swollen in DMF (2 mL) for 20 min. DMF was then removed, 20% piperidine solution in DMF (2 mL) was added and the reaction mixture was shaken at rt for 5 min. After filtration, resin was suspended in the fresh batch of 20% piperidine solution in DMF (2 mL). After 10 min of shaking at rt, the solid was filtered and washed successively with DMF, IPA, THF, THF:MeOH (1:1) and again THF. The solid was dried in vacuo for 24 h.

Catalyst **IV** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-phenylalanine (186 mg).
IR (KBr): ν 1732, 1716 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.69, $f = 0.49$ mmol/g.
Catalyst **V** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-isoleucine (170 mg).
IR (KBr): ν 1732, 1718 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.38, $f = 0.27$ mmol/g.
Catalyst **VI** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-valine (163 mg).
IR (KBr): ν 1732, 1719 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.42, $f = 0.3$ mmol/g.
Catalyst **VII** was prepared according to the general procedure (GPIII) starting from Fmoc-(L)-alanine (149 mg).
IR (KBr): ν 1732, 1716 cm^{-1} (carbonyl bands), N elemental analysis (%): 0.63, $f = 0.45$ mmol/g.

Synthesis of immobilized catalyst XXII

(*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine was prepared starting from quinine according to a published procedure.[34] The solution of obtained (*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine (355 mg, 1.1 mmol) in DCM (4 mL) was cooled to −78°C. Boron tribromide (5.5 mL, 5.49 mmol, 1 M solution in DCM) was added dropwise under an argon atmosphere and the mixture was allowed to warm to rt and stirred for 24 h. 1 M aq. NaOH solution was added at 0°C and the aqueous phase was extracted with DCM (3 × 10 mL). The aqueous phase was neutralized to pH 7 and was extracted with DCM (10 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the crude 4-((*S*)-amino((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) quinolin-6-ol, which was used for the next step without further purification. To a solution of 4-((*S*)-amino((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)quinolin-6-ol (200 mg, 0.65 mmol) in MeOH (1.3 mL) was added di-*tert*-butyl dicarbonate (212 mg, 0.97 mmol) and iodine (16.4 mg, 0.065 mmol). The mixture was stirred at rt for 3 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the aqueous layer was extracted with Et_2O (1 × 5 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 5 mL), dried (Na_2SO_4), filtered and purified by column

chromatography (silica gel, 3–5% MeOH/DCM) to give the product *tert*-butyl ((*S*)-(6-hydroxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methyl)carbamate (181 mg, 68%) as an amorphous off-white solid (NMR spectra are represented in supplementary information, Figure S1).

^{1}H NMR (400 MHz, MeOD) δ 8.62 (d, *J* = 4.7 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 2.6 Hz, 1H), 7.51 (d, *J* = 4.7 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.5 Hz, 1H), 5.93–5.75 (m, 1H), 5.53–5.31 (m, 1H), 5.15–4.96 (m, 2H), 3.67–3.45 (m, 2H), 3.45–3.32 (m, 1H), 3.04–2.81 (m, 2H), 2.59–2.34 (m, 1H), 1.87–1.63 (m, 3H), 1.62–1.47 (m, 1H), 1.37 (s, 9H), 0.98–0.83 (m, 1H).

^{13}C NMR (101 MHz, MeOD) δ 157.9, 157.5, 147.6, 144.3, 142.0, 141.4, 131.5, 130.2, 123.4, 120.8, 115.8, 105.9, 80.9, 60.9, 56.1, 52.3, 42.3, 39.9, 28.6, 28.6, 27.4, 26.3.

HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}N_3O_3$ 410.2438; found 410.2433.

Merrifield resin (200 mg, *f* = 1.02 mmol/g) with KI (3.4 mg, 0.02 mmol) were suspended in 4 mL DMF and allowed to swell for 20 min. *Tert*-butyl ((*S*)-(6-hydroxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)carbamate (100 mg, 0.24 mmol) and sodium hydride (12 mg, 0.31 mmol, 60% in mineral oil) were added to the suspension and the reaction mixture was shaken at 50°C for 48 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

IR (KBr): ν 1706 cm^{-1} (Boc-protecting group carbonyl band before removal).

N elemental analysis (%): 2.54, *f* = 0.6 mmol/g.

Synthesis of the immobilized catalyst ***XXIII***

(*S*)-2-amino-*N*-butyl-3-(4-hydroxyphenyl)propenamide was prepared starting from (L)-phenylalanine according to a published procedure[35] and was used for the next step without further purification. To a solution of obtained (*S*)-2-amino-*N*-butyl-3-(4-hydroxyphenyl)propenamide (415 mg, 1.76 mmol) in MeOH (3.51 mL) was added di-*tert*-butyl dicarbonate (575 mg, 2.63 mmol) and iodine (45 mg, 0.18 mmol). The mixture was stirred at rt for 16 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the aqueous layer was extracted with Et_2O (1 × 10 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 10 mL), dried (Na_2SO_4), filtered and purified by column chromatography (silica gel, 3–4% MeOH/DCM) to give the product *tert*-butyl (*S*)-(1-(butylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (528 mg, 89%) as an off-white solid. All analytical data are in agreement with literature.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.1 Hz, 2H), 6.93 (br. s, 1H), 6.77–6.71 (m, 2H), 5.91 (br. s, 1H), 5.18 (br. s, 1H), 4.21 (q, *J* = 7.3 Hz, 1H), 3.23–3.07 (m, 2H), 3.02–2.86 (m, 2H), 1.42 (s, 9H), 1.39–1.29 (m, 2H), 1.27–1.14 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

Merrifield resin (200 mg, *f* = 1.02 mmol/g) with KI (3.4 mg, 0.02 mmol) were suspended in 4 mL DMF and allowed to swell for 20 min. *Tert*-butyl (*S*)-(1-(butylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (82 mg, 0.24 mmol) and sodium hydride (12 mg, 0.31 mmol, 60% in mineral oil) were added to the suspension and the reaction mixture was shaken at 50°C for 48 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h. Deprotection was performed according to the GP I.

IR (KBr): ν 1671 cm^{-1} (carbonyl band); 1711 cm^{-1} (Boc-protecting group carbonyl band before removing).

N elemental analysis (%): 0.95, *f* = 0.34 mmol/g.

General procedure (GPIV) for the preparation of the immobilized catalysts ***XXIV – XXXI***

A: To a solution of corresponding amino acid (1 eq, 8.7 mmol) in MeOH (9 mL) and 1 M NaOH aq. solution (7 mL) was added di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmol) and iodine (0.22 g, 0.87 mmol). The mixture was stirred at rt for 3 h. Then, sat. aq. $Na_2S_2O_3$ solution was added, and the pH was adjusted to 4 with 1 M HCl aq. solution. The aqueous layer was extracted with DCM (3 × 15 mL). The organic phase was washed with sat. aq. $NaHCO_3$ solution (1 × 15 mL), dried (Na_2SO_4), filtered and purified by column chromatography (silica gel, 10% EtOAc/PE).

Boc-(L)-α-phenylglycine was obtained according to the general procedure (GPIV-A) starting from (L)-α-phenylglycine (1.32 g) as a white solid (1.9 g, 87%). All analytical data are in agreement with literature.[37]

^{1}H NMR (400 MHz, DMSO) δ 12.77 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.46–7.25 (m, 5H), 5.11 (d, J = 8.4 Hz, 1H), 1.39 (s, 9H). $[\alpha]_D^{25}$ = 130 (c 0.2, abs.EtOH).

Boc-(L)-phenylalanine was prepared according to the general procedure (GPIV-A) starting from (L)-phenylalanine (1.44 g) as a white solid (2.1 g, 91%). All analytical data are in agreement with literature.[38]

^{1}H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 7.31–7.17 (m, 5H), 7.09 (d, J = 8.4 Hz, 1H), 4.09 (ddd, J = 10.3, 8.3, 4.5 Hz, 1H), 3.01 (dd, J = 13.8, 4.6 Hz, 1H), 2.82 (dd, J = 13.8, 10.3 Hz, 1H), 1.32 (s, 9H). $[\alpha]_D^{20}$ = 21 (c 0.17, abs.EtOH).

B: (Aminomethylated)polystyrene (500 mg, *f* = 1.2 mmol/g) was suspended in 4 mL DMF and allowed to swell for 20 min. Boc-protected amino acid (1.2 eq), HOBt (1.3 eq, 105 mg), 4-dimethylaminopyridine (0.1 eq, 7.3 mg) and *N*,*N*′-diisopropylcarbodiimide (1.2 eq, 113 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 48 h. The solid was filtered, washed with DMF and directed to end-capping step. Deprotection was performed according to the GP I.

End-capping with acetic anhydride. The solid was resuspended in 4 mL DMF. Acetic anhydride (2 eq, 113 μL) and pyridine (2 eq, 97 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

End-capping with pivaloyl chloride. The solid was resuspended in 4 mL DMF. Pivaloyl chloride (2 eq, 147 μL) and triethylamine (2 eq, 167 μL) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

End-capping with methyl iodide. The solid was resuspended in 4 mL DMF. Methyl iodide (4 eq, 149 μL) and potassium carbonate (2 eq, 166 mg) were added to the suspension and the reaction mixture was shaken at 60°C for 3 h. The solid was filtered and washed successively with DMF, H_2O, MeOH, MeOH:THF (1:1) and THF. The solid was dried in vacuo for 24 h.

Catalyst **XXIV** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-methionine (180 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.28 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.42 mmol/g.

Catalyst **XXV** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-*O*-benzyl-(L)-serine (213 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1723 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.23 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.39 mmol/g.

Catalyst **XXVI** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-2-propargylglycine (154 mg).

IR (KBr) ν 1657 cm^{-1} (broad carbonyl band); 1721 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.34 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.46 mmol/g.

Catalyst **XXVII** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-leucine (167 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1719 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.36 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.48 mmol/g.

Catalyst **XXVIIIa** was prepared according to the general procedure (GPIV-B) using end-capping with acetic anhydride starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1652 cm^{-1} (broad carbonyl band); 1718 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.4 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.5 mmol/g.

Catalyst **XXVIIIb** was prepared according to the general procedure (GPIV-B) using end-capping with methyl iodide starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1657 cm^{-1} (broad carbonyl band); 1720 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.5 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.58 mmol/g.

Catalyst **XXVIIIc** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-alanine (136 mg).

IR (KBr) ν 1655 cm^{-1} (broad carbonyl band); 1723 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.51 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.59 mmol/g.

Catalyst **XXIX** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-phenylalanine (191 mg).

IR (KBr) ν 1681 cm^{-1} (broad carbonyl band); 1716 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.23 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.39 mmol/g.

Catalyst **XXX** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-α-phenylglycine (181 mg).

IR (KBr) ν 1651 cm^{-1} (broad carbonyl band); 1719 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.22 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.38 mmol/g.

Catalyst **XXXI** was prepared according to the general procedure (GPIV-B) using end-capping with pivaloyl chloride starting from Boc-(L)-α-*tert*-butylglycine (167 mg).

IR (KBr) ν 1676 cm^{-1} (broad carbonyl band); 1717 cm^{-1} (Boc-protecting group carbonyl band before removing), N elemental analysis (%): 2.28 ((aminomethylated)polystyrene contains 1.69% of N), *f* = 0.42 mmol/g.

[2,3]-Wittig Rearrangement Reaction of 2-(Cinnamyloxy)cyclohexan-1-one with the Polystyrene-Supported Catalyst XXIX

To a solution of 2-(cinnamyloxy)cyclohexan-1-one (0.24 mmol, 55 mg) in $CDCl_3$ (1.2 mL), catalyst **XXIX** (*f* = 0.38 mmol/g, 0.048 mmol, 126 mg) and *p-NBA* (0.048 mmol, 8 mg) were added. The reaction mixture was shaken at 50°C for 16 h. The polystyrene-supported catalyst was removed by filtration and the sat. aq. $NaHCO_3$ (5 mL) was added to the supernatant. Then, the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the product **2** (46 mg, 84%) as a white amorphous solid. All analytical data are in agreement with literature (HPLC chromatograms are represented in supplementary information, Figure S2).[26]

Major diastereomer *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35°C, λ = 210 nm; t_R (major) = 7.7 min and t_R (minor) = 11.8 min].

Minor diastereomer *ee* 86% [Chiralcel OJ-H column, hexane/*i*PrOH 7:3, flow rate 1 mL/min, 35°C, λ = 210 nm; t_R (major) = 34.6 min and t_R (minor) = 9.8 min].

Recycling experiment

To a solution of 2-(cinnamyloxy)cyclohexan-1-one in $CDCl_3$ (0.2 M), catalyst **XXVIIIc** or **XXIX** (20 mol %) and *p-NBA* (20 mol %) were added. The reaction mixture was shaken at 50°C for 16 h. The polystyrene-supported catalyst was removed by filtration and washed successively with $CHCl_3$ and MeOH. The solid was dried in vacuo for 24 h before the next portion of reactants was added. Deactivation of the catalyst could be observed by color changing as it turned brown from light yellow.

Curriculum vitae

Personal data

Name:	Aleksandra Murre
Date of birth:	21.01.1995
Place of birth:	Tallinn, Estonia
Citizenship:	Estonian

Contact data

E-mail:	alexandra.murre@gmail.com

Education

2018–...	Tallinn University of Technology, Chemistry and Biotechnology, PhD
2016–2018	Tallinn University of Technology, Chemistry and Biotechnology, MSc (*cum laude*)
2013–2016	Tallinn University of Technology, Chemistry and Biotechnology, BSc (*cum laude*)
2001–2013	Tallinn Tynismae Science School

Language competence

Russian	Native
Estonian	Fluent
English	Fluent

Professional employment

2023–...	Tallinn University, School of Natural Sciences and Health, visiting teacher
2018–...	Tallinn University of Technology, School of Science, Department of Chemistry and Biotechnology, early-stage researcher
Summer 2017	Cambrex Tallinn OÜ, applied researcher
Summer 2016	Cambrex Tallinn OÜ, applied researcher

Professional associations

2019–...	The Estonian Chemical Society, member

Honours and awards

2020	Zonta scholarship, Estonian National Culture Foundation
2020	AS Liwathon E.O.S. Doctoral Study Scholarship, TalTech Development Fund, Estonia
2019	Dora Plus T1.1 short-term mobility scholarship, Archimedes Foundation, Estonia
2018	Ene Silla named scholarship
2018	Tamkivi scholarship, Estonian National Culture Foundation
2017	Jaan Poska named scholarship
2017	Rotalia foundation (USA) scholarship
2016	Cambrex Tallinn Bachelor Study scholarship, TalTech Development Fund, Estonia
2016	The national student research competition, 2nd place (Bachelor thesis in natural sciences or engineering)

Teaching experience and supervision

Fall 2019	Organic Chemistry I, exercise tutorials (undergraduate course)
Spring 2020	Organic Chemistry II, exercise tutorials (undergraduate course)
Fall 2021	Organic Chemistry I, exercise tutorials (undergraduate course)

Elulookirjeldus

Isikuandmed

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Hariduskäik

2018–…	Tallinna Tehnikaülikool, Keemia ja biotehnoloogia, PhD
2016–2018	Tallinna Tehnikaülikool, Keemia ja biotehnoloogia, MSc (*cum laude*)
2013–2016	Tallinna Tehnikaülikool, Keemia ja biotehnoloogia, BSc (*cum laude*)
2001–2013	Tallinna Tõnismäe Reaalkool

Keelteoskus

Vene keel	Emakeel
Eesti keel	Kõrgtase
Inglise keel	Kõrgtase

Teenistuskäik

2023–…	Tallinna Ülikool, Loodus- ja terviseteaduste instituut, külalislektor
2018–…	Tallinna Tehnikaülikool, Loodusteaduskond, Keemia ja biotehnoloogia instituut, nooremteadur
Suvi 2017	Cambrex Tallinn OÜ, keemik
Suvi 2016	Cambrex Tallinn OÜ, keemik

Kuuluvus erialaühingutesse

2019–…	Eesti Keemiaselts, liige

Teaduspreemiad ja tunnustused

2020	Zonta stipendium, Eesti Rahvuskultuuri Fond
2020	AS Liwathon E.O.S. doktoriõppe stipendium, SA Tallinna Tehnikaülikooli arengufond
2019	Dora Pluss T1.1 lühiajalise õpirände stipendium (SA Archimedes, Eesti)
2018	Ene Silla nimeline stipendium
2018	Tamkivi stipendium, Eesti Rahvuskultuuri Fond
2017	Jaan Poska nimeline stipendium
2017	Rotalia foundation (USA) stipendium
2016	Cambrex Tallinn AS bakalaureuseõppe stipendium, SA Tallinna Tehnikaülikooli arengufond
2016	Üliõpilaste teadustööde riikliku konkurss loodusteaduste ja tehnika valdkonnas rakenduskõrgharidusõppe ja bakalaureuseõppe üliõpilaste astmes, II preemia

Õpetamiskogemus ja juhendamine

Sügis 2019	Orgaaniline keemia I, harjutustunnid (bakalaureuseõpe)
Kevad 2020	Orgaaniline keemia II, harjutustunnid (bakalaureuseõpe)
Sügis 2021	Orgaaniline keemia I, harjutustunnid (bakalaureuseõpe)

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